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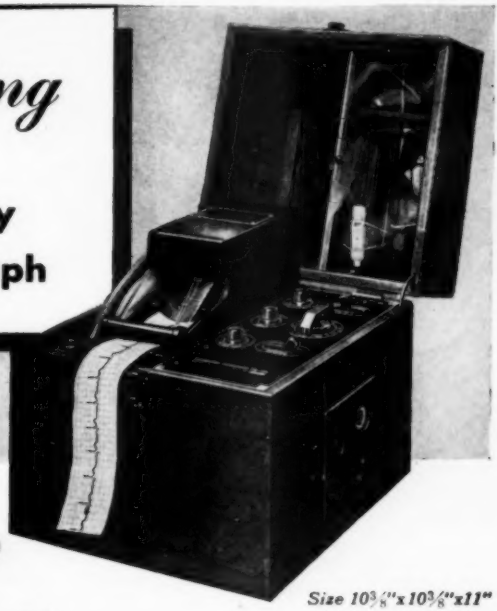

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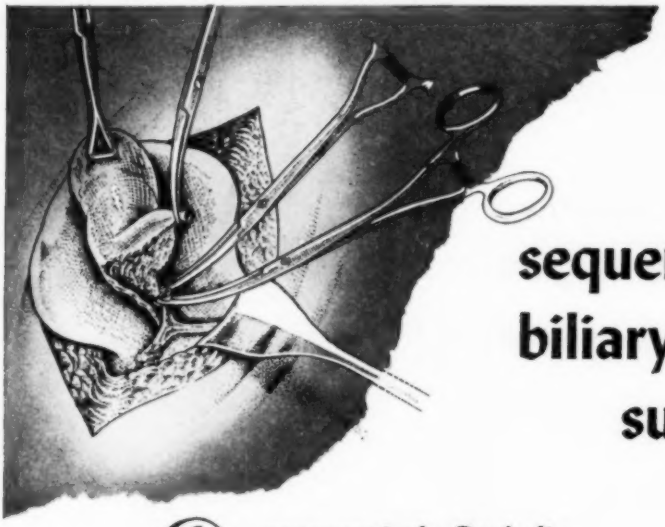

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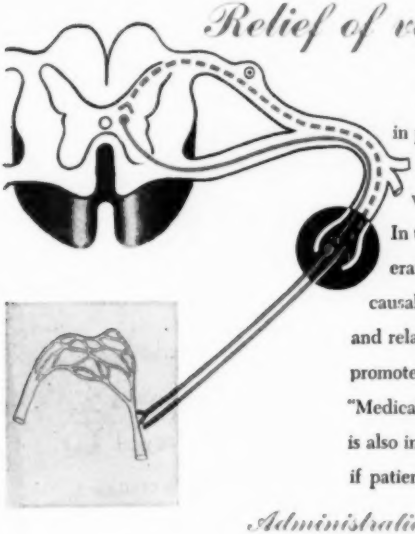

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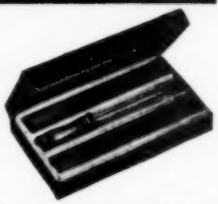

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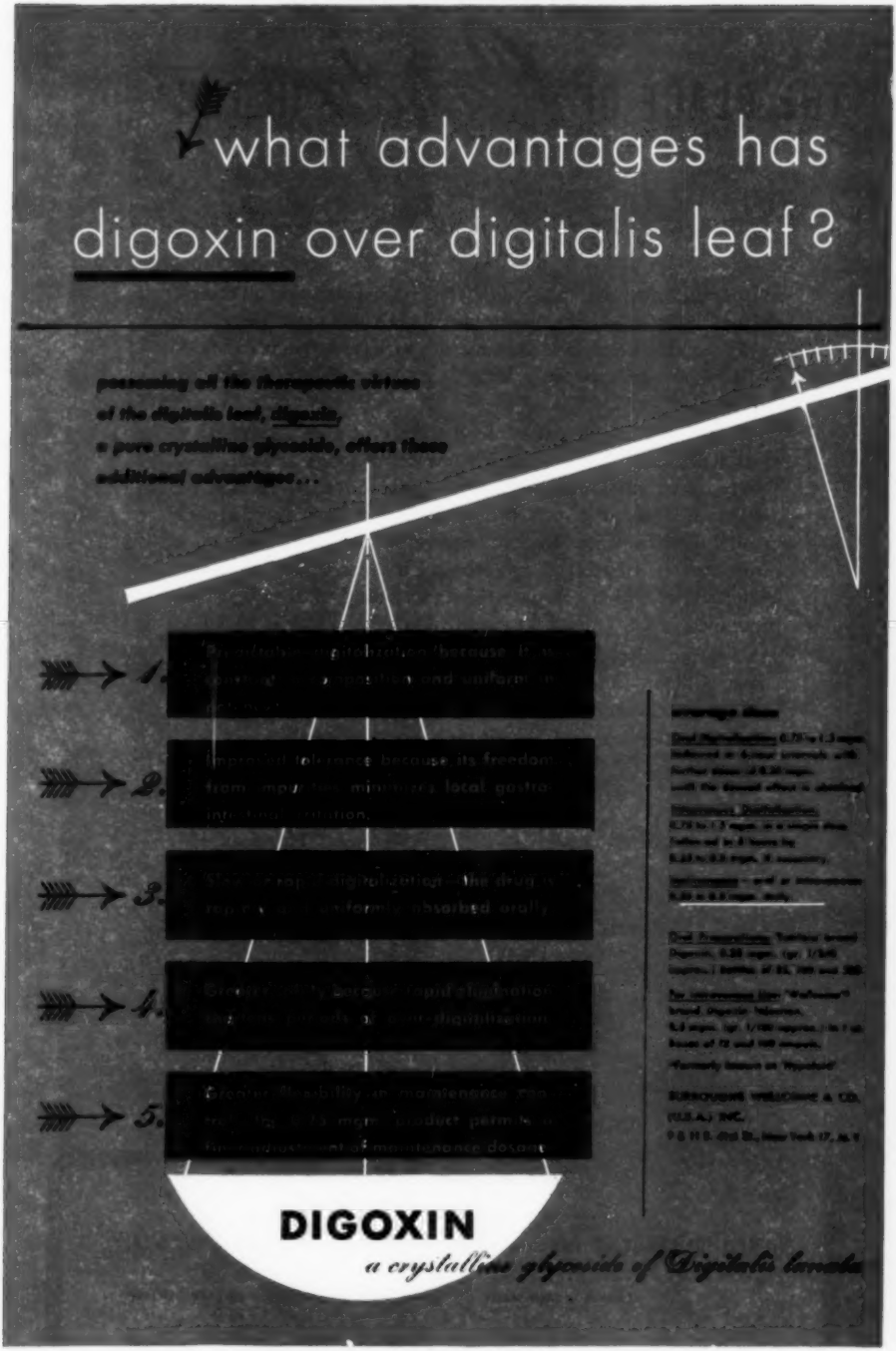
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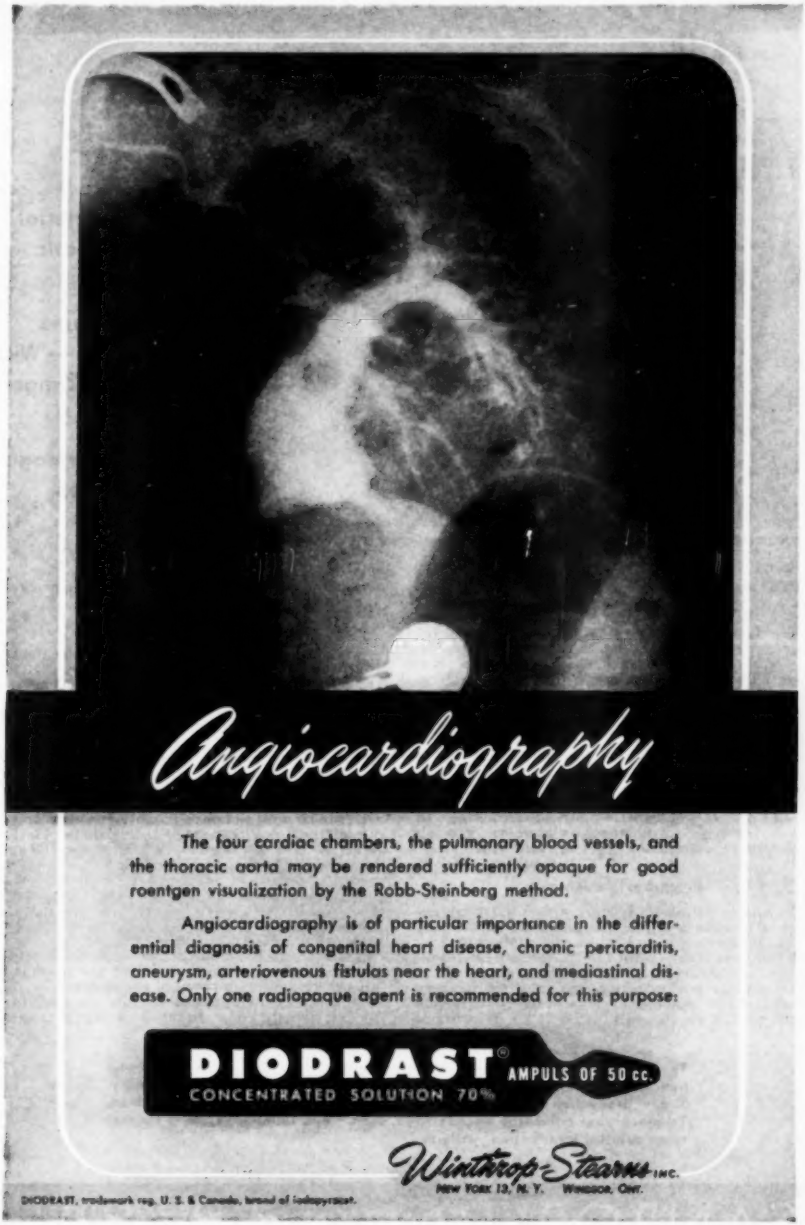
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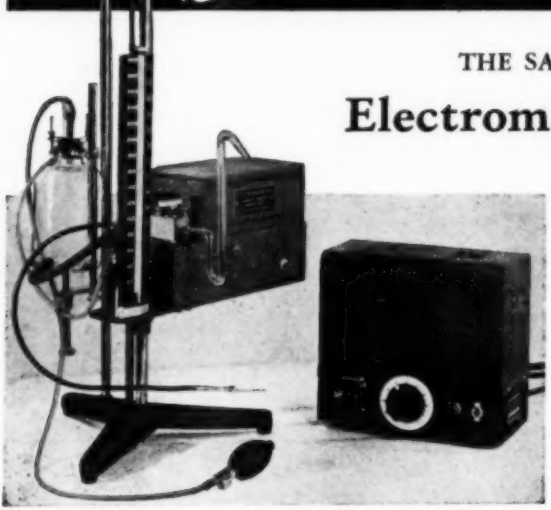

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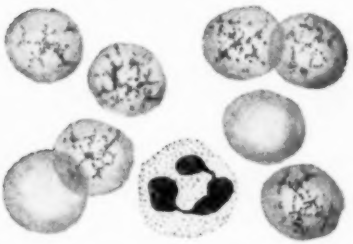

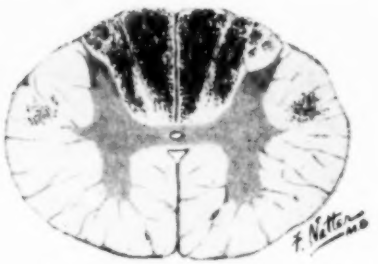

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1. Brewster, J. M., U. S. Naval Med. Bull. **49**: 1-11, January-February 1949.

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*Hueper, W. C.: Medical Clinics of North America, May 1949.

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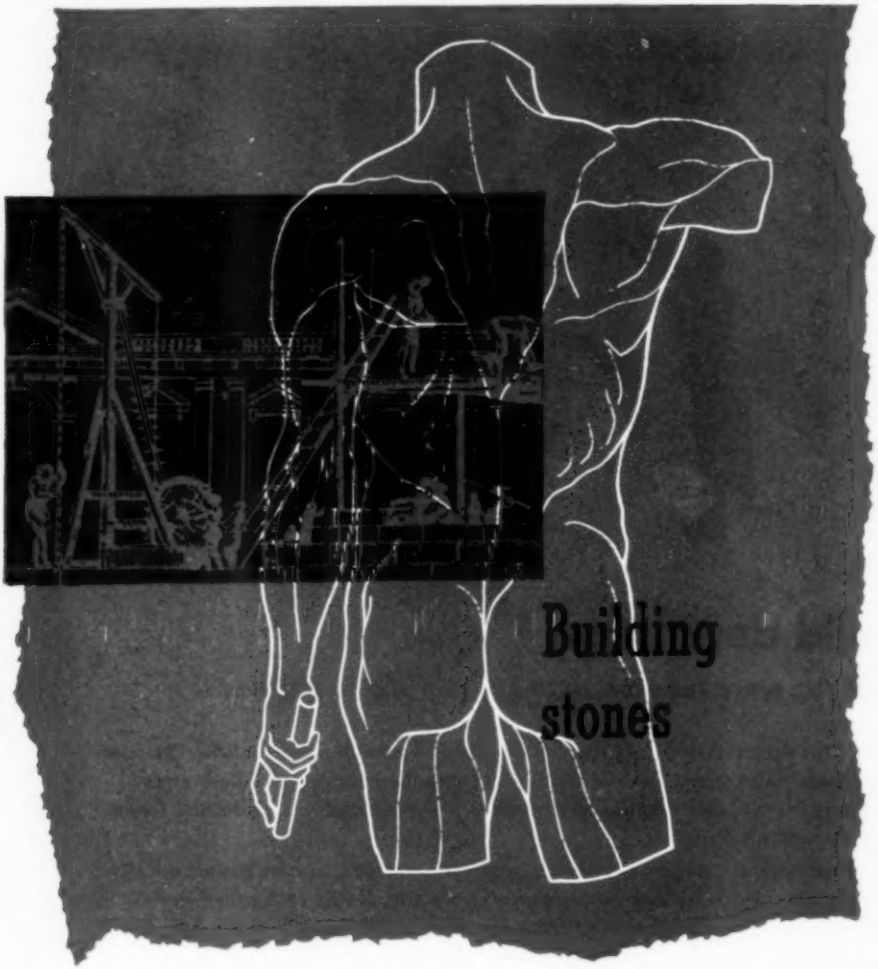

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1. Ivy, A. C., and Goetzl, F. R. (1943), d-Desoxyephedrine; A Review, War Med., 3:60, January.
2. Davidoff, E. (1943), A Comparison of the Stimulating Effect of Amphetamine, Dextroamphetamine and Dextro-N-Methyl Amphetamine (Dextro-Desoxyephedrine), Med. Rec., 156:422, July.

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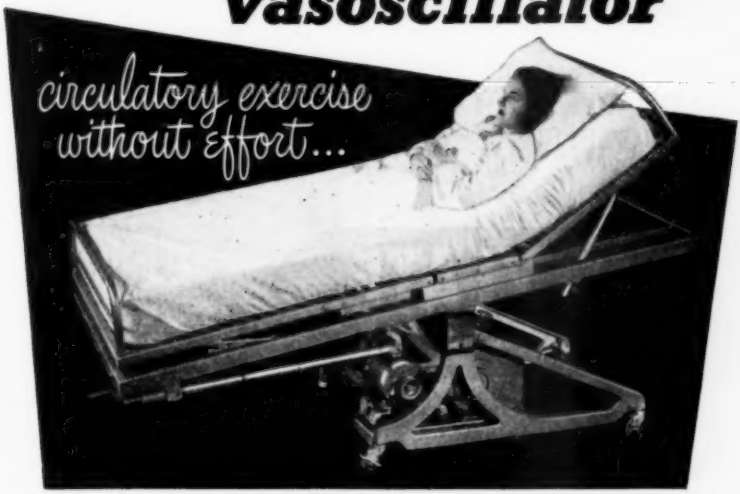

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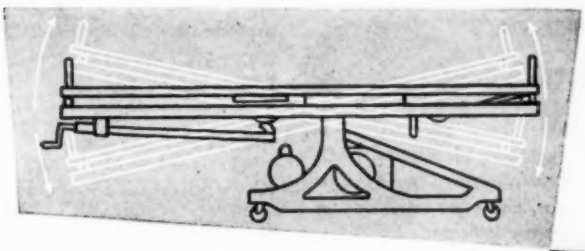

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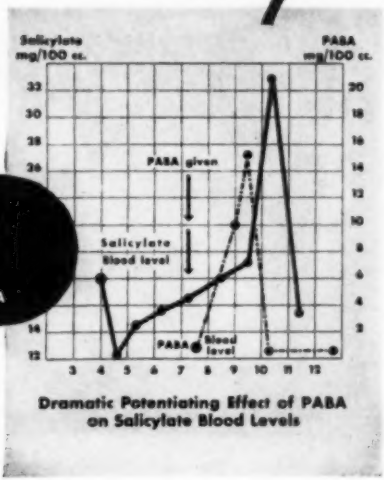

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1. Dry, T. J.; Butt, H. R., and Scheifley, C. H.: Proc. Staff Meet., Mayo Clin. 21: 497 (1946). 2. Béïsle, M.: Union méd. du Canada 77: 392 (1948). 3. Salassa, R. M.; Bollman, J. L., and Dry, T. J.: J. Lab. & Clin. Med. 33: 1393 (1948). 4. Rosenblum, H., and Fraser, L. E.: Proc. Soc. Exper. Biol. & Med. 65: 178 (1947).

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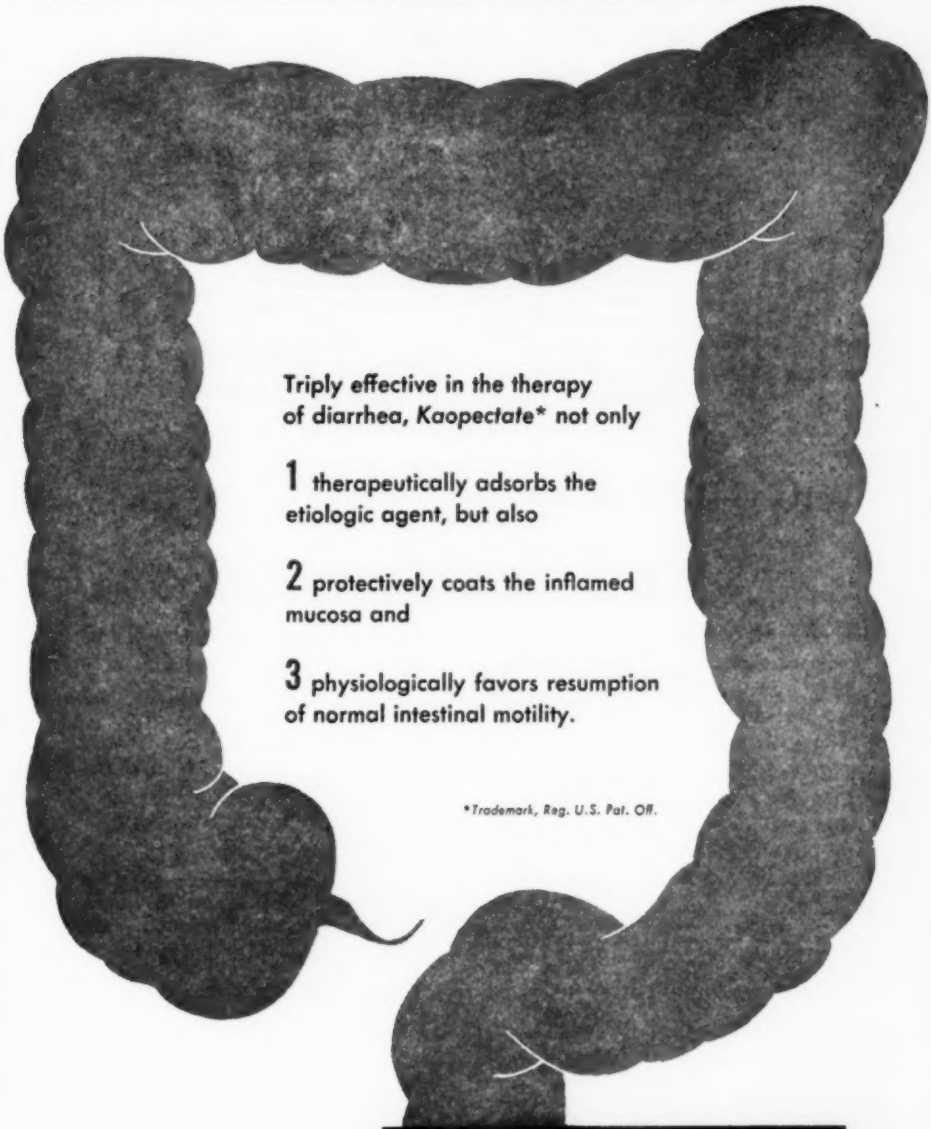

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1. Grimson, Marzoni, Reardon and Hendrix: Ann. of Surg., 127: 5, May, 1948.
2. Reich, N. E.: Med. Times, Jan., 1949.

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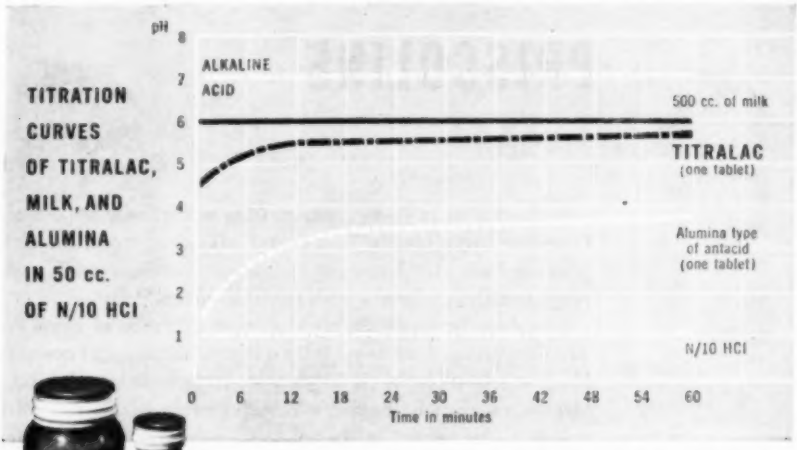

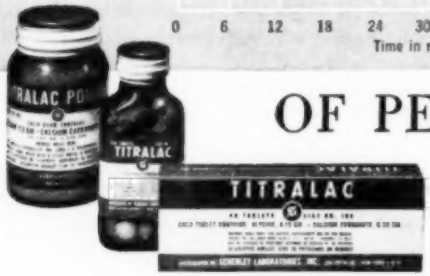

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REFERENCES

1. Rossett, N. E., and Flexner, J.: Ann. Int. Med. 18: 193 (1944). 2. Freezer, C. R. E.; Gibson, C. S., and Matthews, E.: Guy's Hosp. Reports 78: 191 (1928). 3. Aaron, A. H.; Lipp, W. F., and Milch, E.: J. A. M. A. 139: 514 (Feb. 19) 1949. 4. Kirsner, J. B., and Palmer, W. L.: Illinois M. J. 94: 357 (Dec.) 1948. 5. Kimball, S.: in Practice of Medicine (Tice). Hagerstown, Md., W. F. Prior Company, Inc., 1948, p. 210. 6. Special Article: M. Times 76: 10 (Jan.) 1948.

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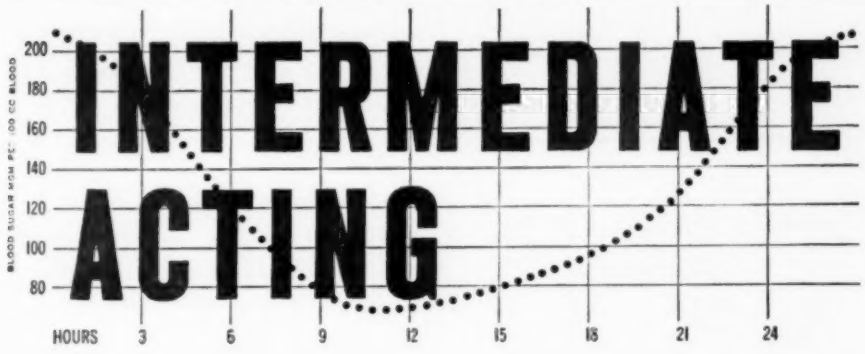

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1. Rohr, J.H., and Colwell, A.R.: Arch. Int. Med. 82:54, 1948.
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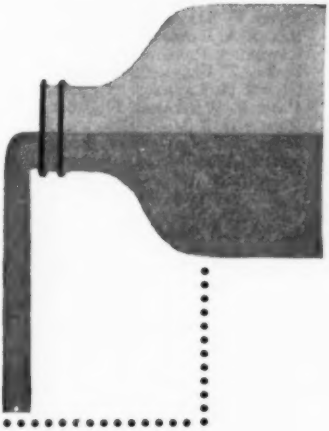

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EMOTIONAL FACTORS IN ORGANIC DISEASE *

By WILLIAM C. MENNINGER, M.D., F.A.C.P., *Topeka, Kansas*

THE scope implied in the title—emotional factors in organic disease—is comparable to that of a discussion of "chemical factors in organic disease." This presentation is therefore made on the assumption that this group of internists with superior ability and experience, recognizes that emotional factors may indirectly cause and frequently do aggravate organic lesions. The psychiatrist's responsibility should be to indicate the relation of certain types of emotions to the organic process and what the internist can and should do about them. Therefore, it shall be my attempt to point out some of the relationships of emotion and soma, to report briefly some of the basic knowledge acquired to date in this area, and finally, to present a sketchy classification of the emotional components in various types of organic disease, with suggestions regarding their management.

In the many current articles dealing with this general subject, one occasionally finds that a psychiatrist tends to be critical of the internist's efforts. Perhaps he judges the internist by his failures in complicated situations and allows too little credit for his successes. Occasionally an internist may belittle a psychiatrist for his lack of knowledge of internal medicine and the chemistry and physiology of physical disease. Both are probably correct. The real need is for the provision of better integration of the various bodies of knowledge and for methods of communicating these to each other.

The recent emphasis on the psychosomatic approach in illness has been helpful to all of us, regardless of the fact that the word itself connotes the very dichotomy which it is intended to obviate. Perhaps this was necessary to indicate that our previous approaches tended to be either chiefly or completely psychologic *or* somatic.

Many of us believe that the term, and more particularly the concept, might advisedly be elaborated further to include the prefix socio-, referring to the fact that man's social relationships, interests and activities are also important components of any disability he develops. Presumably the social concept

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was included in "psycho-," although social factors are distinct from the unconscious psychological stimuli operative in illness. A threatened or actual job disruption, economic insecurity, social ostracism and many other circumstances related to one's social status may play a significant rôle in an illness, either in its etiology or recovery. Until such a time as medical education can correct the deficiencies and the prevalent point of view about illness, the concept of a socio-psycho-somatic approach will at least serve to emphasize the holistic nature of our patients and the necessity to consider these three aspects of every case.

Emotions

Basic in the consideration of this problem is the meaning of the terms emotion and emotional factors. They are extremely complex phenomena. In addition to being merely feeling tones, they represent the drives or the forces that not only make us live but determine the type of life we lead. They include the many variations of love, hate, and fear. The individual's behavior, i.e. his total socio-psycho-somatic reaction, may indicate deficiency or excess in his emotional response.

The effect on the body of conscious emotional attitudes stimulated by external situations is familiar even to the layman. He is aware that there is a very definite connection between the way he feels and how his body behaves. The physical and chemical reactions in an emotional response to a temporary external situation, whether this be anger or fear, are so well known as to merit no discussion here. The accompanying physiological responses to such situations rarely if ever bring an individual to a physician.

There are, on the other hand, many trying environmental situations to which the individual adjusts himself by suppressing his feeling, i.e., consciously holding his emotional reaction in check. Such suppressed emotion can produce various physiological symptoms. For example, instead of being able to express freely and directly his hostility or resentment, he keeps it under control with the subsequent development of a headache. An individual who refuses to admit his homesickness may develop gastric symptoms. Another who dares not face his sense of insecurity may have heartburn.

In such instances, by the psychological mechanism of conversion, the personality channels the suppressed emotion, by way of the vegetative nervous system, into some type of physical symptom.

For some years psychiatrists used the term "conversion" to apply only to those cases in which the emotion arising from an unrecognized psychological conflict became pinned down in some part of the body that was under voluntary control. Such "hysterical" symptoms could be seen and demonstrated even though there was no organic pathology: paralysis of the arm, anesthesia, or a loss of the voice. Most psychiatrists now however consider all disorder of function of an organ of the body related to an emotional conflict as a conversion symptom.

Suppression, as illustrated above, is a voluntary effort to control one's

conscious emotional feelings. In considering the total influence of emotions on the body, one must include the even more powerful effect of completely unconscious conflicts.

In the course of infant and childhood development, every individual must give up certain totally unacceptable "wishes" or "desires." On the basis of our psychoanalytic knowledge, these are known to be totally excluded from consciousness by an automatic psychological mechanism termed "repression." They are forced into the unconscious portion of the personality, an area which ordinarily is not accessible to the individual through any conscious effort. Even after their exclusion from consciousness, such desires create a "conflict" by seeking to gain expression. These infantile wishes exert great pressures but conscious forces mobilize to prevent them from coming into awareness or being directly expressed. These conflicts then become encysted foci within the personality. If sufficiently strong, they may escape their encystment to gain expression in disguised forms as symptoms. They continue to be motivating factors in the life of the individual, entirely unrecognized by him. In the great majority of instances they are associated with infantile and childhood experiences, particularly in relation to the basic emotions of love and hate, of self-interest and self-indulgence.

Through the experiences of the early developmental situation, every individual takes on particular personality traits or characteristics. It is now well recognized that there are various types of so-called personality or character types which are related to the methods the individual uses to gain satisfaction, the extent of his dependency or independency, the capacities he has to form relationships with other people and the particular types of these relationships. These factors lay the groundwork for subsequent neurotic symptomatology.

The psychiatrist is interested in attempting to understand the individual's total behavior whether this is in relation to the external environment or in terms of his own internal psychological and physical makeup. The interreaction of psyche and soma is not difficult to understand in such situations as the response to fear or rage. It becomes far more complicated, however, when the emotional responses arise from unconscious conflicts. Physicians do fully recognize that psychological conflict may be expressed in bizarre behavior or bizarre ideas typified by the psychosis. On the other hand, the conflict may use an "organ language" rather than intra-psychic language and be expressed in physical symptoms. These manifestations may actually alternate: there are numerous reports of patients recovering from a psychosis on the development of an organic illness, and on the other hand an individual may recover from an organic disease only to develop a psychosis.

We are thus at a stage in our knowledge where we can be sure that the unconscious psychological forces directly influence the function of the soma, and specifically certain organs, even though as yet the data at hand are meager. The interpretation of psychodynamics in medicine as in other sciences is far ahead of our ability to apply them in many concrete cases. As Jelliffe [1] once

stated, "In geo-physics, much is known of the dynamics of earthquakes but no one yet has stopped one; similarly the science of physical chemistry is aware of the enormous quantities of energy locked up in a shovel full of sand, but as yet no one has been able to boil an egg with it. When it comes to clinical problems of internal medicine, the application of these psychological principles, while not so far from application as the hopes of controlling earthquakes, or cooking with sand, are still in need of research."

Dr. Jelliffe continued further, "The study of the psychoneuroses is paving the way for an understanding of many diseases of the body with which internal medicine is involved, and which begin silently or subtly as neurotic disturbances. This has been known for centuries. In the neurotic stages of maladjustment (organ neuroses) the processes are still reversible. But after a certain number of years of such faulty adaptations, the processes become irreversible."

Organic Disease

As intimated above, many physicians are as yet not acquainted with unconscious determinants in illness. Consequently they are perplexed when the conscious or reality situation does not seem sufficient to account for the causation or the aggravation of the organic condition. The social situation often does not explain the total reaction; it never explains the effects of the unconscious emotional conflict.

Although a considerable amount of data has been accumulated in regard to the unconscious psychological factors in various types of organic disease, it is still inadequate. In spite of these deficiencies, it may be of interest to indicate briefly those illnesses about which there is some knowledge of a specific emotional component.

With regard to various types of disorders of the *cardiovascular* system, the psychodynamics of hypertension [2, 3] are probably the best understood. In addition to the probability of a constitutional vasomotor instability, the psychological component is based upon excessive and inhibited hostile impulses. Unconscious resentment or anger is repressed so that it fails to gain direct expression and is converted into hypertension. The increased blood pressure which is a protective reaction in acute states of fear or anger to preserve homeostasis becomes inappropriate when continued as a long term adaptive pattern of reaction.

Studies of coronary disease [4] also suggest that sometimes this illness is a reflection of powerful feelings of hate which have been totally repressed by a man who is strongly attached to the father and hostile to the mother.

Study of migraine [5] indicates that this illness most frequently occurs in compulsive individuals who, because of unconscious needs, present a personality characterized by conscientiousness, meticulousness, perfectionism, inflexibility. These qualities lead to frequent frustrations and tension and set the stage for the headaches.

Among the disorders of the *gastrointestinal system*, the psychological

conflicts associated with peptic ulcer have been studied in most detail. According to one theory, [6] the initial symptoms of peptic ulcer appear in association with an intense craving for food. This craving is often, if not always, equated with a need or desire for love, which is repressed but unsatisfied. The infantile relationship between the wish to receive, to be taken care of, to be loved, and the function of eating as such, that the patient's physiology as an adult is always acting on the basis that it is preparing for or receiving food. Another type of conflict [7, 8] explains the peptic ulcer as an attempt to resolve unconscious hostility and to gain security through eating.

In so-called mucous or spastic colitis, [9, 10] the diarrhea is symbolic of a hostile act; it serves as a psychological substitute for giving something of real value. Along with an unconscious need to receive and take, is the feeling of obligation to give something in exchange. On the other hand, constipation can be an expression of resistance against the obligation to give. The gastrointestinal tract is especially suitable for the expression of the psychological equivalents of its three physiologic functions—in-taking, retaining and eliminating. This occurs when the normal expression of these personality traits is interfered with through unconscious psychological conflicts.

Among *respiratory conditions* which have been studied psychoanalytically, most is perhaps understood about asthma [11] in which the psychological conflict is a repressed longing, basically for the mother. This desire is frustrated or threatened with frustration and the attack is symbolic of the protest of a crying spell. The conflict may operate independently of or together with specific allergic sensitiveness.

Among the *endocrinological disorders*, a study which has been made of diabetes [12] suggests that in addition to the constitutional factors, such patients may show unusually strong unconscious wishes to remain dependent in order to be taken care of. The frequency of emotional trauma at the onset of diabetes is well known, as is also the fact that emotions can very markedly affect the course of the illness.

The development of hyperthyroidism is associated with the loss or threat of loss of a cardinal interpersonal relationship.[13] Such patients had a childhood in which they felt less wanted than a sibling but by special effort became the winner of parental affection. This pattern of striving for affection continues after emancipation from the rival sibling relationship. They are inordinately jealous of affection and tend to bind themselves to some person by smothering solicitude. If their offers are rebuffed, the childhood insecurity is revived and they become resentful and depressed.

The organic disorders of the *genito-urinary system* have received as yet scant psychological study although psychic factors in various functional disorders are relatively transparent. Dysmenorrhea is recognized in many instances as an unconscious denial of femininity. Sterility in women, as well as habitual abortions, suggest an unconscious hatred of the mother and the femininity she represents or a fear of pregnancy, a purely feminine capability. Impotency in men is most often related to an unconscious rejection of

the masculine rôle. In other instances it can be an act of aggression towards the wife, or an expression of fear of women.

The study of unconscious psychological conflicts in a few other organic conditions has led to some tentative formulations. Some cases of *rheumatoid arthritis,* [14] in addition to those of inherited, traumatic or infectious origin, show a psychodynamic background of chronically inhibited hostility as a reaction to the earliest helpless dependence on the mother. In women patients the personality rejects the female rôle and unconsciously wishes to be a man. In many instances, there is an excessive need to do for others. This serves both to discharge hostility and to deny her own extreme desire for dependence.

The psychological significance of *low back pain* [15] is implied in the famous G. I. remark of "Oh my aching back." It symbolized his resentment against the forced assumption of the unwanted responsibilities and heavy burdens, more emotional than physical, that were his to carry.

Various *skin diseases* [16, 17] have been studied and frequently represent, as did the famous Scarlet Letter, an external manifestation of an unconscious conflict related to sexuality. They thus simultaneously may express a longing, frustration and/or guilt.

Significance of Emotional Reaction in Organic Disease

By over-simplification, one can classify the rôle of emotions in various types of organ changes as follows:

1. *Emotions as a Causative Factor in Organic Disease:* Emotions do not cause organic disease directly. Unconscious psychological conflicts express themselves by way of the vegetative nervous system by interfering with normal functions in specific organs. A long-standing disorder in the function of an organ may lead to definite organic change. The pathological damage is not per se a neurotic or symbolic symptom.

In the chain of events leading to an organic lesion, the unconscious psychological conflicts are the first link, and, therefore, are of extreme significance in understanding the disease. This does not mean, however, that the treatment should be solely or even chiefly psychological. Practical palliative therapy is often indicated that may range from aspirin to sedatives, to the radical procedures of lobotomy, vagotomy, or splanchnicectomy, whereby the patient's disability is relieved by dulling or short-circuiting the emotional stimuli.

However, the use of these measures should not exclude corrective or curative therapy of a psychological nature. Reports of such operative procedures often indicate the tendency to ignore the fundamental psychological conflict as well as the need for subsequent psychotherapeutic efforts to resolve it. This may even account for certain failures in the effectiveness of surgical procedures.

2. *Emotional Factor As a Conspicuous Symptom in Organic Disease:* In

another group of organic diseases the emotions are intimately related to the development of the disorder in some patients, to the production of specific symptomatology in others, and enter into the question of treatment in nearly all patients.[18] As yet we do not know or claim that the emotions have a specific etiological rôle and they may be less important than such factors as heredity, constitution or infection. Essential hypertension, migraine, rheumatoid arthritis and mucous colitis serve as examples of this relationship.

During the treatment of this type of illness, the alert physician becomes aware of characteristic attitudes and behavior in his patients which interfere with recovery. These are well described by Hart [19] under the term of "resistance symptoms." He listed procrastination in seeking medical advice, indulging in self-treatment, sabotaging treatment through ignoring the prescribed diet, forgetting medications, breaking appointments, limiting treatment, obstructing examination by a vague, incoherent prolonged recital of trivial complaints, being hypersensitive about and intolerant to a personality study, and refusing to recognize significant indications of insecurity or conflict.

The average physician can hardly be expected to explore unconscious conflicts. He can, however, recognize "resistance symptoms" and the conscious emotional attitude of the patient. One of his most important therapeutic tools is allowing time to listen to his patient's aeration of his feelings about himself, his illness and his interpersonal relationships. In many instances this is the most effective therapy that the patient can receive. Sometimes even stubborn symptoms disappear with a sympathetic hearing. The alert physician can also help the patient see and accept the emotional relationship without his feeling that he is getting a brush off or is a little queer!

3. *Emotional Factors As a Complication of Organic Disease:* Emotional factors complicate organic disease when: (a) Organic disease develops in a neurotic personality; (b) events with emotional significance to the patient take place during the course of his organic illness; and (c) when because of misinformation about or fear of his disease, the patient develops manifest or latent anxiety.

Such complications can arise in any type of illness. When a neurotic individual suffers from an organic disease it may be extremely difficult, if not impossible, to determine which of his symptoms are organic and which are neurotic. It is, nevertheless, important for the physician to be sufficiently skillful in the investigation of psychological data to identify the emotional factors and try to treat them properly. All too often he aggravates an illness in this type of patient by ill advised statements, misplaced emphases, inadequate or misunderstood explanations.[20]

Every physician has seen many situations in which current events in the life of a patient greatly affected the course of his disease, for better or for worse. What happens to the patient's family, to his job, his economic status, his plans—with the resultant fears, frustrations, and disappointments—are

all of potential importance in the progress of his illness. This is the reason for the physician to assume responsibility for determining the patient's sociological as well as psychological status.

As to the third complication, when the patient lacks proper information and therefore becomes anxious about his illness, the solution is often relatively simple. Too often, however, the physician is unaware of the misinformation which is the cause of his patient's anxiety. When the prognosis is favorable this is less of a problem. Any misconceptions should be checked and clarified. When the prognosis is poor, the physician may be taxed to his maximum capacity to give all the support possible to help the patient in accepting the inevitable.

4. *Emotional Factors in the Acceptance of Physical Handicaps:* In so many organic illnesses the patient has to learn to live with his disability, whether it be a cardiac condition, carcinoma, or some other chronic illness or a physical deformity. Where convalescence is unduly slow, far too often psychological factors are the cause. Medication, massage and exercise are not sufficient to help the patient accept his handicap and build a new life within necessary restrictions. A sound psychological principle is to extend activity as much as possible and limit prohibitions to the minimum. Too often the reverse is true: physicians tend to limit the activity of their patients by prohibiting social and business activities, alcohol, tobacco, exercise, etc. Ideally the physician should suggest new, positive goals which would point to the future adjustment of the patient to his handicap.

The psychological impact of either progressive or stationary sequelae of an acute disease process is often overlooked. Whether it is paralysis or deformity or a limiting disability that does not show, the patient's future depends largely on the psychological devices used to help him live with it. The physician should be the chief therapist in aiding the patient to accept the necessary changes required in his social existence.

Patients also have families to whom the doctor automatically has a deep responsibility. In most instances, it is the family who makes the major contribution toward the alleviation or, on the other hand, intensifies the emotional factor in the patient's organic disease.

In summary, the investigations of the rôle of the emotional factors in a few specific organic diseases have been intensive but the positive data accumulated are minimal. Even so, these findings have opened broad vistas for future study. In retrospect, during recent years, most of the important steps in the progress of medicine have come through biological investigations. Possibly future advances may come more and more through psychological investigations of the reaction which we call illness. Certainly there are no greener pastures for research. When such studies can be undertaken, we may find that within the *next* 25 years the most fruitful steps of progress in the field of medicine will come through the illumination of the psychological aspects of what we now term organic disease.

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PULMONARY DISEASE MANIFESTATIONS OF ANKYLOSING SPONDYLARTHRITIS *

By K. A. Hamilton, M.B., B.Ch., F.A.C.P., *Edmonton, Alberta, Canada*

During the past few years, owing to my association with the Department of Veterans' Affairs of Canada, the opportunity has arisen to observe some results of the operation of disease processes over long periods of time. The object of this contribution to the subject of ankylosing spondylarthritis is to set forth some observations and conclusions, with interpretation in terms of anatomy, physiology and pathology. Some clinical and therapeutic suggestions are also submitted.

In ankylosing spondylarthritis there is widespread impairment of joint function. The disease is commonly regarded as being one of the apophyseal joints of the spine and of the sacro-iliacs. Limb joints often suffer as well. Its well recognized end result is fusion of apophyseal and sacro-iliac joints, with rigidity and disturbance of posture and locomotion. Costo-vertebral joint disease resulting in fusion also occurs and leads to disturbance of respiratory function and to acute, recurrent and chronic pulmonary disease. This paper will focus attention upon the respiratory disease manifestations, which are part of the entity.

Textbook descriptions of ankylosing spondylarthritis list rigidity of the thoracic cage as an outstanding clinical manifestation. Breathing is described as entirely diaphragmatic, with the ribs fixed in expiration, the result of involvement of the costo-vertebral joints. Among frequent complications are reported pneumonia, and in those who have had the disease for some time, pulmonary tuberculosis in up to 25 per cent.[1]

Miller [2] reports that acute inflammation of the small joints of the dorsal region may immobilize the ribs long before ankylosis has developed, so that the breathing becomes abdominal.

Diminished expansion of the chest is referred to by Oppenheimer.[3] He considers this suggestive of involvement of the costo-vertebral joints and reports its presence in 62 per cent of the cases in his stages II and III.

Consideration of anatomy, physiology and pathology, as these sciences apply to the ribs and respiratory mechanics, may help explain some features of ankylosing spondylarthritis that have, I think, not been explained or at least not emphasized previously.

Anatomical and Physiological Considerations. The mechanics of rib movement during respiration is a matter of elementary anatomy and physiology. Standard works should be referred to for details concerning fulcrum-

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From the Treatment Services of the Department of Veterans Affairs of Canada and the Department of Medicine of the University of Alberta Faculty of Medicine, Edmonton, Alberta.

age, leverage, axes of rib movement and motor power.[4] Briefly, the scalene muscles are fixators of the first rib. During inspiration the external intercostal muscles use this rib as an anchorage to exert their contractile power to move the second to the tenth ribs upward, outward and forward. The sterno-manubrial joint permits of this mass movement and the thoracic cage alters in shape and volume. Expiration uses two thoracic mechanical components which operate to reverse the thoracic alterations of inspiration. One is passive and consists of recessive recoil. The other is active and derives its motor power from contraction of the internal intercostal muscles. For most respiratory purposes the active component is not called into action, being held in reserve to serve unusual respiratory needs as in dyspnea and cough.

Thoracic respiration will be referred to as being activated by the scalene-intercostal motor system, essential for normal inspiration, but supplementary according to need, to assist passive thoracic recoil during expiration.

In addition to thoracic movement, another mechanism operates in respiration. This is the diaphragm-abdominal muscle system. The diaphragm acts like a piston in a cylinder to create intrathoracic vacuum in inspiration and compression in expiration. During inspiration the diaphragm's active contraction is coördinated with reciprocal inhibition and relaxation of the abdominal muscles. During expiration the diaphragm-abdominal muscle system goes into reverse. In the accomplishment of this there are two components, passive and active. The one consists of inhibition and relaxation of the contracted diaphragm with resumption of tone by the abdominal muscles. This serves ordinary respiratory needs. The other consists of active contraction of the abdominal muscles to compress the abdominal contents and push the reciprocally inhibited diaphragm upward to achieve intrathoracic compression. This active expiratory component operates to serve extraordinary respiratory needs.

Cough is a variant of respiration, adapted to serve the specific purpose of bronchial clearage. Like normal respiration it may be excited by reflex and volitional stimuli. It consists of an inspiratory effort, followed by a varyingly violent expiratory effort, or series of efforts, according to the intensity of the exciting stimulus. The principle of explosion operates by virtue of coördination of the glottis, which opens at the height of compression of the thoracic contents. The active expiratory components of respiration, thoracic and abdominal, are employed in cough. They provide the power needed to achieve the thoracic compression for explosive release. Scalene-intercostal and diaphragm-abdominal muscle power systems are integrated and coördinated for this purpose.

The cough mechanism, for efficiency, requires the participation of both of the active components of expiration, thoracic and abdominal. Either component unassisted by the other is inadequate. If the active thoracic component should be in abeyance the force of the ascending diaphragm, in cough, is transmitted to and partially spent against the inside of the thoracic

cage, tending to expand it. Such a situation obtains in intercostal muscle paralysis, where inefficient cough leads to pulmonary complications. If the active abdominal component should be in abeyance adequate compressive force for efficient cough can not be achieved by thoracic action alone and again pulmonary complications tend to develop.

In order that there shall be efficient cough the ribs must be mobile. Otherwise the active thoracic expiratory component can not operate efficiently to provide the sudden vigorous thoracic devexity necessary for counter-thrust against the ascending diaphragm, which must obtain for the achievement of adequate intrathoracic compression. This is fundamental to the principle of explosion on which cough depends.

Pathological Considerations. Effective rib movement and hence effective active thoracic expiration requires mobile costo-vertebral joints. When these are strangulated by inflammatory reaction, cough efficiency is impaired and in such circumstances pulmonary pathology tends to develop, because cough is complementary to ciliary and bronchial movement in the defensive process of bronchial clearage. Ciliary and bronchial movements may be regarded as the sweepers and cough the shoveler in this clearage organization. Active thoracic retraction in cough is probably most essential for clearage of upper lobe bronchi, especially should the supine posture be protractedly assumed with negation of gravity's usual force.

Reference to anatomical textbook drawings must emphasize the proximity of relationship of costo-vertebral to apophyseal joints in the dorsal region. In ankylosing spondylarthritis both sets of articulations suffer inflammatory reaction. The ligamentous bindings of the spine are a continuum and such names as are applied to the various parts and slips which support the costo-vertebral joints are artificial and academic, even if needed for descriptive purposes. These ligaments participate in the strangulating process which produces apophyseal and costo-vertebral joint immobilization. Strangulation of the costo-vertebral joints interferes with the efficiency of thoracic inspiration and expiration so that chest expansion is greatly reduced. This limitation of function is relatively unimportant, except insofar as it affects the efficiency of cough, the great defensive device for protection of the lungs against injury arising from the action of noxious agents within the airways.

When cough is rendered inefficient for any reason, atelectasis is apt to occur. It is frequently seen after abdominal operations and is then due to inhibition of cough by pain arising in the abdominal wall or cavity. Such pain impairs the efficiency of the diaphragm-abdominal muscle power system and basal atelectasis may result. Spinal or general anesthesia may contribute by suspending the contractility and tone of the abdominal muscles during the period of its action. The immediate cause of this type of atelectasis is a bronchial plug, formed of inspissated mucus or mucopus, which can not be ejected because of enfeeblement of the cough explosion. Hypersecretion by the goblet cells of the bronchial mucosa, irritated by intrabronchial noxious agents contributes to the formation of the plug. Only too

frequently the post-operative patient with atelectasis will reveal that he had "a cold" or the like, shortly before or at the time of his abdominal operation.

Bronchial plugging is rapidly followed by zonal atelectasis. Pneumonitis then ensues, the result of infection by resident infective agents, which thrive under the cultural conditions provided by the plug and the zone of collapse.

Clinical Considerations. Atelectasis with associated pneumonitis and pleuritis is common, recurrent and disabling throughout the long course of ankylosing spondylarthritis. Prior to the introduction of the sulfonamides and penicillin it was not infrequently fatal.[5] It culminates as a result of a concatenation of events. These can be traced back to a fundamental predisposing cause, which is costo-vertebral joint inflammation.

In a normal person "a cold" is usually a trivial self-limiting disease. In the presence of ankylosing spondylarthritis, on the other hand, it may be troublesome and serious, because it is frequently followed by atelectasis, pneumonitis, pleuritis and their sequelae. These sequelae are pleural adhesions and pulmonary fibrosis, which in turn tend mechanically to compound already existent respiratory embarrassment.

Abdominal operations and spinal anesthetics are particularly hazardous to persons who have ankylosing spondylarthritis. The thorax being frozen by disease at the costo-vertebral joints, suspension of abdominal muscle action leaves cough in abeyance during the period of the anesthetic and varyingly enfeebled for the duration of incisional or intra-abdominal pain, postoperatively.

Patients who have ankylosing spondylarthritis need effective and rational medical aid when conditions prevail to induce pulmonary complications. They are unable to deal effectively with "colds" by themselves. Awareness of the likelihood of important pulmonary complications should help in management by consideration of chemotherapy or perhaps bronchoscopic aspiration according to indications presented as a result of adequate diagnostic study. They also need careful pre- and postoperative consideration when abdominal operations are contemplated and needfully effected.

Pulmonary fibrosis revealed by roentgen-ray should call for complete and systematic physical and radiological examination of other areas and functions of the body beyond the limits of the thorax. The possibility of the existence of ankylosing spondylarthritis should be given consideration and elaborated by historical, physical and radiological study. Perhaps some spondylarthritics who are considered to have tuberculosis do not have this serious disease, but are suffering from much more benign post-atelectatic pulmonary fibrosis. Certainly such clinical problems would seem to be entitled to most persistent and intensive bacteriological studies before being considered tuberculous.

In treatment of ankylosing spondylarthritis emphasis has been placed on the prevention of postural deformity and limitation of spine movement. This emphasis has largely resulted in the disease being considered an orthopedic problem. Unquestionably this clinical attitude has its merits, but only

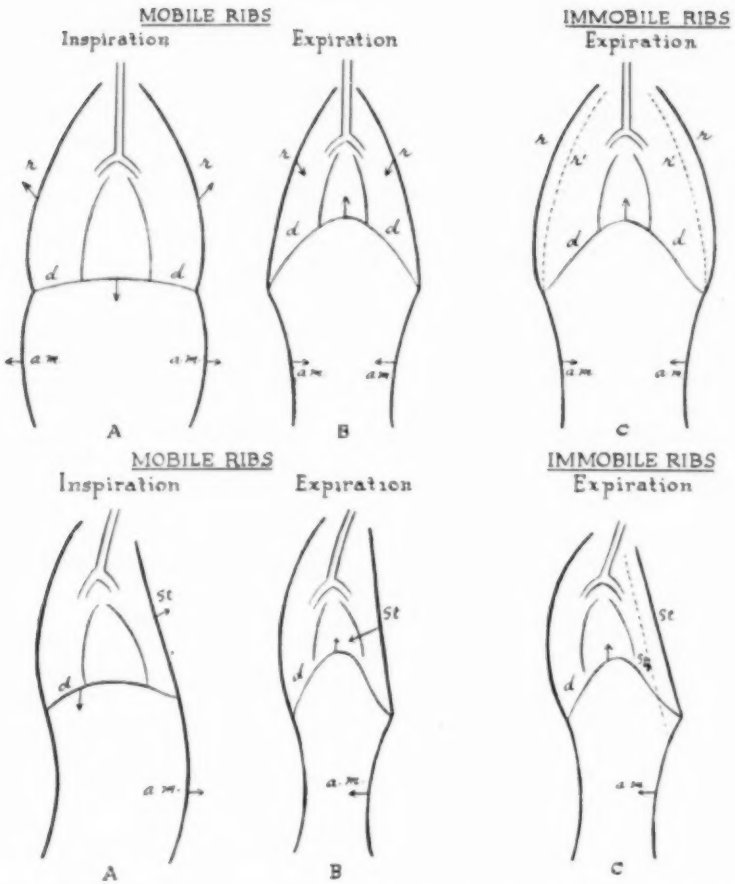


FIG. 1. Diagrammatic representation of positions of ribs, diaphragm and abdominal muscles in full inspiration and full expiration.

upper—antero-posterior projection
lower—lateral projection
r —ribs
d —diaphragm
a.m. —abdominal muscles
st. —sternum

Diagrams at right represent defective rib movement, as obtains in ankylosing spondylarthritis. Interrupted lines represent position of ribs r^1 and sternum st_1 in this disease, and distance between interrupted and continuous lines the amount by which thoracic mobility is impaired.

too often the respiratory manifestations of the disease are under-assessed or over-looked in the orthopedic clinic. Sometimes casts applied for the prevention or correction of flexion deformity may be prejudicial to the already embarrassed respiratory mechanisms. Further in treatment, it is as necessary to effect measures to ensure that the costo-vertebral joints shall remain as mobile as possible as long as possible, as it is to help ensure that the apophyseal joints shall remain in such condition.

The diaphragm-abdominal muscle system can take care of the ordinary respiratory needs in this disease, but it can not, unassisted by thoracic movement maintain an efficient and very essential cough mechanism. Thoracic breathing training and exercises therefore constitute an important aspect of preventive medicine among sufferers from the disease under consideration.

The following case summaries are submitted in exemplification of the principles elaborated above. They are from the files of the Department of Veterans' Affairs and the records of the University of Alberta Hospital.

Case 1. A young woman with painless ankylosing spondylarthritis who was never aware of the existence of the disease until it was discovered as a result of investigation for the cause of persistent cough following a "cold."

A physician's wife, 24 years of age, was seen in mid November, 1946. She had had a cough for two months which began with a "head cold." She was afraid that she might have tuberculosis. She was short of breath on moderate exertion and her rib movement was minimal. Evidence of heart disease was not found. Her spine was rigid throughout. Shoulder joint movement was slightly impaired. There was no evidence of disease within the chest on physical examination and a roentgenogram showed only heavy bronchovascular markings, though increased shadows at the right base suggested that a small area of atelectasis had been present and had almost completely resolved. Her past history was negative except for very frequent sore throats between the ages of 12 and 18.

Radiological studies of spine and sacro-iliac joints confirmed the clinical diagnosis of ankylosing spondylarthritis. Sacro-iliacs were fused.

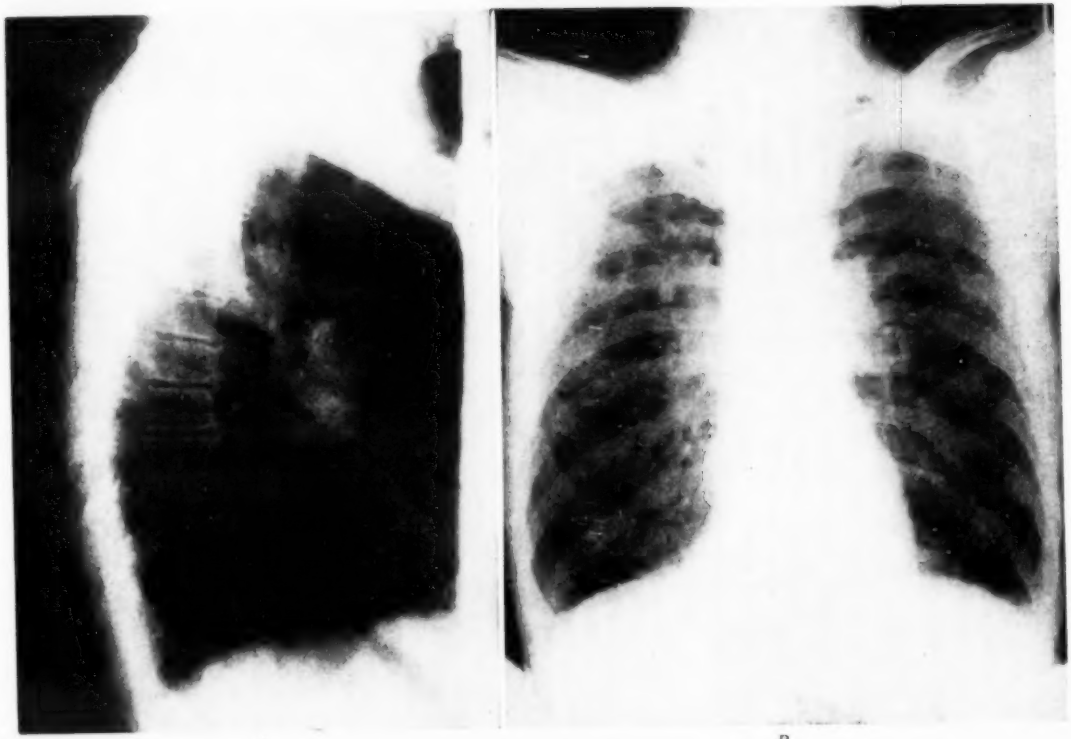
She was seen again on October 13, 1947, having again contracted a "head cold" which was followed by a persistent cough for several weeks. A shadow at the right lung base on the roentgen-ray film suggested the presence of a small area of atelectasis.

Back or joint pain had never been experienced by this young patient, though she had noted difficulty in stooping due to inflexibility of her back. Search for a cause for persistent cough led to the discovery of spinal arthritis.

Case 2. An elderly man who had had recurrent non-specific pulmonary infection with pleural involvement dating from 1916. Pulmonary infection complicated surgery and spinal anesthesia during his earlier admissions to hospital. Ankylosing spondylarthritis was unsuspected until it had reached an advanced stage.

1939 (June). This patient first entered hospital at age 58 for repair of a left inguinal hernia. He had lost all digits of hands and feet in 1937 by amputation after frost bite. Little record was made of the state of his respiratory system except mention that his chest moved "slightly." Operation under spinal anesthesia was followed directly by a brisk febrile coughing illness of 10 days' duration. No further useful clinical details were recorded and no chest film was taken.

1940 (February). Toe stump callouses were excised under spinal anesthesia. Low fever was recorded for several days postoperatively without satisfactory clinical details being noted.



A B

FIG. 2. *Case 2.* (*W. R. J.*) *A.* 1946, spine. Ankylotic disease with calcification and kyphotic deformity. *B.* 1947, chest. Pleuro-pulmonary residua 31 years after onset of recurrent pulmonary infections.

1944 (February). He had an open reduction and wiring under spinal anesthesia for fractured left patella. Pre-operatively he was stated to be suffering from "chronic bronchitis" and a chest film was taken. This was reported as indicating the presence of old diaphragmatic pleurisy with fixation of both diaphragms. Postoperatively he had a febrile coughing illness for six days. He received therapeutic doses of sulfathiazole and cough mixture during this episode.

1946 (June). Admitted to a medical service for investigation prior to admission to a veterans' home as a permanently disabled person. He stated that he had been coughing persistently for three or four years and that he had had six attacks of pleurisy since 1916. Gross impairment of chest excursion and râles and wheezing were recorded. Spine showed complete absence of flexibility. Chest film was compared with that of 1944 and was reported to show diaphragmatic flattening and thickening of costophrenic angle, left, with enlargement of hilar shadows. Markings in upper halves of both lung fields, particularly in the left, were described as accentuated. Radiologist's conclusion was "fibrosis as a result of previous inflammatory disease." Roentgenograms of the spine showed generalized osteoporosis, calcification along the anterior margins of the vertebral bodies, dorsal, and considerable lipping with fusion of sacro-iliacs. Sputum studies were negative for *M. tuberculosis. H. influenzae* and *Klebsiella* were cultured in numbers. On completion of the investigation he was transferred to the veterans' home, diagnosed advanced ankylosing spondylarthritis with pulmonary fibrosis due to recurrent non-specific pulmonary infection.

1947 (March). Admitted for dermatitis and conjunctivitis following administration of sulfathiazole for a recent "chest cold." Skin complications promptly resolved with stoppage of the drug.

Case 3. A 54 year old farmer with advanced ankylosing spondylarthritis. Gross postural deformity in flexion and immobility of the rib cage. History of recurrent pulmonary infection from 1929 associated with, and also occurring independently of abdominal surgery. Benign pulmonary fibrosis simulating tuberculosis and bronchiectasis.

1933–34 (October–March). The patient was admitted to the orthopedic service because he could not work on account of back pain and stiffness of about a year's duration. He had had typhoid fever in 1915 and his gall-bladder had been removed in 1929 at another hospital. He had had pleurisy with effusion on the right side after the operation, necessitating prolonged hospitalization and convalescence. Aspirated fluid was then negative for tuberculosis by guinea pig test.

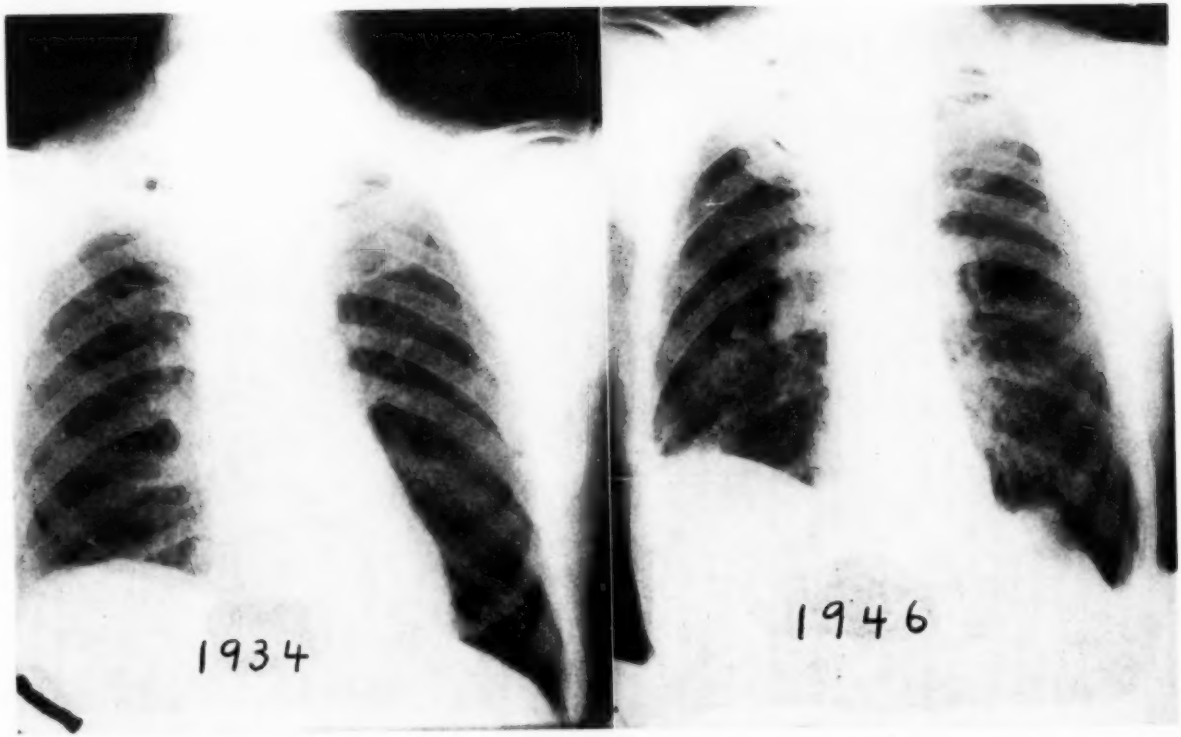
A roentgenogram of his spine was interpreted as "osteoarthritis," though a clinician expressed the opinion that his disease was rheumatoid arthritis of the spine and some limb joints. Several teeth were extracted and a tonsillectomy performed following which he received physical treatment measures as an in-patient.

Some three months after admission and while still in hospital he developed left pleurisy with a grating friction rub following a "cold." He had an ineffective cough. A chest film showed a high right diaphragm with retraction of the right thorax, which may have been a sequel of the postoperative pleural disease of 1929. Several sputum smears were negative for tuberculosis and no attempt was made to culture pyogenic organisms.

When his acute symptoms subsided he was considered to have chronic pleurisy and was transferred to a hospital for chronic illness.

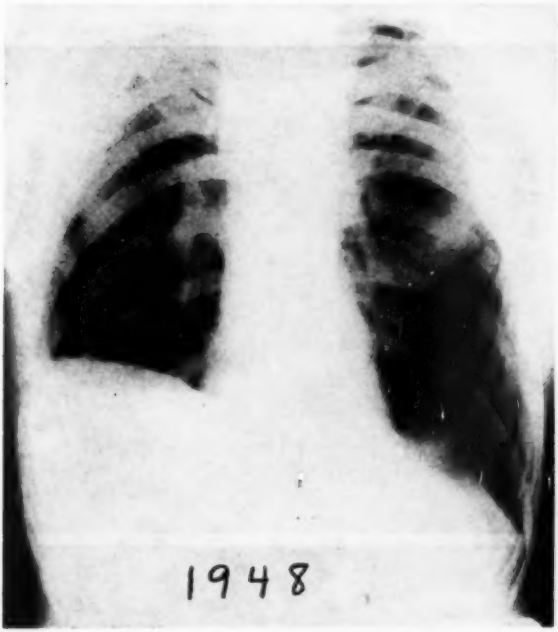
1934–35 (October–March). Re-admitted for pain in the back and several limb joints. A diffuse toxic goiter was discovered and treated by a two-stage operation. No detail as to respiratory status can be found, and roentgenographic study of the chest was apparently not made. No evidence of a postoperative chest complication is recorded. He left the hospital still having backache and stiffness.

1937 (November). Re-admission for gonorrhea. In addition to a description of the local disease manifestations, cough, basal râles and shortness of breath are



A B

FIG. 3. *Case 3.* (*A. B.*) *A.* 1934, high fixed right diaphragm and accentuated bronchovascular markings. *B.* 1946, patchy basal infiltration bilaterally and density at right apex. Right diaphragm high and fixed; left diaphragm "tented." This film was taken during an episode of acute febrile pulmonary disease, which responded to sulfonamide therapy.



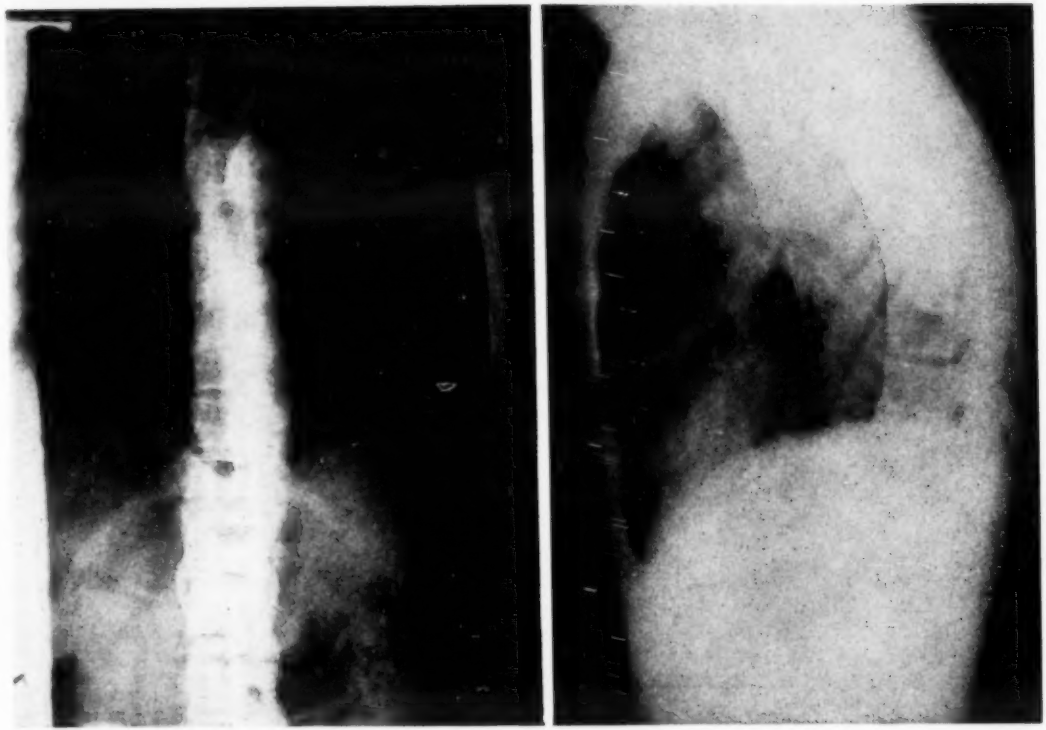
C

FIG. 3. *Case 3. C.* 1948, film during a period of freedom from acute pulmonary symptoms. Shows residual fibrotic and adhesive changes.

mentioned in the record. No roentgenographic studies were made. Back, shoulders and elbows were reported as stiff and painful.

Apparently he maintained tolerable health with considerable skeletal incapacity from 1937 to mid 1944. Then he developed what he was told was bronchopneumonia and was in a rural hospital for two weeks. On discharge he moved to a neighboring province to convalesce and in December, 1944 had to enter hospital there for another attack of what was called bronchopneumonia. Following this illness he coughed for several weeks. In February, 1945 he was operated upon there for cancer of the stomach, but no such disease was found. Postoperatively he had a brisk illness with chills, headache and sweating which was accompanied and followed by persistent cough and prolonged weakness. On account of these symptoms he was referred to a tuberculosis clinic and there reported as having active tuberculous pulmonary disease by radiological criteria. A few sputum studies for tuberculosis were negative. In view of sanatorium care being recommended he was sent back to Alberta. These were the circumstances leading up to another re-admission.

1945 (July–August). Re-admission as a tuberculosis suspect for investigation in view of suspicious apical shadows. Posture was described as stooped, with immobile back and ribs. Râles were audible at the left apex and base posteriorly. Vital capacity 1500 c.c. Chest film showed elevation of right diaphragm as previously, with heavy hilar shadows and dense striations into both bases. A "cloudy" right



A *B*

FIG. 4. *Case 3.* (*A. B.*) *A.* 1945, spine, showing bambooing in lumbar region and ankylotic disease in dorsal region. *B.* 1948, spine, lateral projection showing kyphotic deformity and ankylotic disease in lower dorsal region.

apex and increased density overlying the left diaphragm were reported. A negative statement regarding cavitation was made and the radiologist's conclusion was "possible tuberculosis" at right apex and bilateral basal bronchiectasis. Spine studies were then made and described as showing advanced Marie-Strümpell type of arthritis, with calcification of anterior and lateral spinal ligaments and complete fusion of sacro-iliac joints.

Kahn test was negative and sputum cultures grew only *Streptococcus viridans* and *Staphylococcus albus*. Numerous smear examinations were reported negative for *M. tuberculosis* and three guinea pigs inoculated with sputum failed to develop this disease.

1945 (August). Re-admitted for dyspepsia, which after thorough investigation was considered benign and functional. No significant changes in pulmonary or skeletal disease were found.

1946 (August). Re-admitted for treatment of a febrile respiratory illness, characterized by cough, breathlessness and bilateral anterior chest pain of pleuritic type. Fixed high right diaphragm and basal fibrosis were again reported radiologically and apical infiltration previously reported was considered to have increased in density and extent. Therapeutic doses of sulfadiazine were followed by prompt subsidence of fever and acute symptoms. No significant pyogenic organisms were cultured and several smears were negative for *M. tuberculosis*. Sputum was also negative for *M. tuberculosis* by culture and guinea pig tests.

1946 (September). Re-admission for infectious hepatitis. No further pulmonary or skeletal disease changes were noted.

1947 (May). Re-admission for genital dermatitis. Study of pulmonary and skeletal disease revealed no significant progression.

1948 (January). Brought into hospital for further study in the absence of new symptoms or signs. Lipiodol bronchograms did not reveal evidence of bronchiectasis.

Summary

In the long course of ankylosing spondylarthritis episodes of pleuro-pulmonary disease are frequent and recurrent. They stem from a common factor which is disease of the costo-vertebral joints. Cough as a pulmonary defensive reaction is emphasized. The importance of costo-vertebral joint mobility for cough efficiency is stressed and explanation is given in terms of anatomy, physiology and pathology for some pulmonary manifestations of the disease. Attention is directed to hazardous situations which may arise out of "colds," abdominal operations and anesthetics. Suggestions for improvement in management of the disease are made.

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XIPHOSTERNAL CRUNCH: AN ANALYSIS OF 106 CASES AMONG 3,224 ARMY SEPARATEES *

By Louis Schwab, M.D., *Weston, Massachusetts,* Gordon L. Smiley, M.D., *Ann Arbor, Michigan* and Werner P. Meyn, M.D., *St. Louis, Missouri*

Introduction

Solis-Cohen [1] has recently called attention to a peculiar heart sound heard in the tricuspid area among normal individuals, which is designated as the xiphosternal crunch. His report emphasized that:

1. It occurred in 17.8 per cent of 4,982 normal Army inductees and in 21.1 per cent of the last 3,115 of this same group who were studied more carefully. It is apparently a normal functional sound.

2. It is commonly misinterpreted as indicating mitral or tricuspid regurgitation, pericarditis or congenital heart disease.

3. It is described in only one of the standard texts on physical diagnosis.

Solis-Cohen's exhaustive review of the literature reveals that since 1817 39 descriptions of sounds, probably identical with the xiphosternal crunch, have appeared. In spite of this interest in the sound in the past, it is apparently not recognized with the frequency that its incidence warrants.

The purpose of the present report is: (1) To further establish the incidence of the sound. (2) To define the physical type in which the sound is most commonly heard. (3) To further describe the sound itself. (4) To suggest a possible mechanism for its production. (5) To again emphasize the importance of recognizing the xiphosternal crunch as a common functional sound, to be differentiated carefully from the sounds of pathologic significance heard in this area. This is of particular importance to medical personnel in the armed forces who are often concerned with screening large groups of individuals during routine physical examinations. Here, the correct interpretation of functional heart sounds takes on real numerical importance, and can result in the salvage of a large group for useful military service who otherwise would be disqualified.

Method of Study

All of the data were obtained during the course of routine examinations of personnel being separated from the Army at the Separation Center, Jefferson Barracks, Missouri in November, 1945. Any of the observations which are entirely subjective were made only after having established a mutual agreement between the examiners as to the term to be applied to any given variation of the sound.

* Received for publication March 4, 1948.

The criterion for designating the sound as a xiphosternal crunch was simply: a systolic sound * of a crunching or spitting nature heard best at a point immediately to the left and above the xiphoid process, in the absence of signs of organic heart disease.

The first heart sound in this area is characteristically more harsh and less muffled than the corresponding sound at the apex. This sound quality is closely similar to the least audible xiphosternal crunches, and a clear cut distinction is often impossible. The authors have included in this series only those sounds meeting the above criterion that were felt to be unquestionably adventitious sounds. It is clearly recognized that this entirely subjective criterion limits the value of this series in attempting to determine the incidence of this sound.

Due to the rigid time limitations required by the separation process, extensive physical examinations, electrocardiograms and roentgen-ray studies were not feasible.

Results and Comment

The results of the study are summarized in table 1.

1. *Incidence:* The over all incidence of the sound, 3.3 per cent, in this study is at wide variance with that recorded by Solis-Cohen,[1] namely, 21.1 per cent. At least three factors should be considered in explaining this difference:

a. The most important cause of the discrepancy is undoubtedly the extremely subjective nature of the data recorded. The present study records only those sounds that to the average ear would be considered without question to be an abnormal sound. Less rigid criteria would undoubtedly result in a greater incidence.

b. The two groups of men examined differed fundamentally in that Solis-Cohen examined a heterogeneous group of *inductees,* prior to their acceptance for service, whereas the present report is derived from examination of *separatees.* This series is, therefore, a highly selected one, in that it represented a group much above the average in general physical fitness.

In this connection it should be pointed out that there is at least a suspicion that part of the discrepancy between the two incidences could be explained by the possibility that many individuals were rejected from service at the draft board or induction station level because of misinterpreted xiphosternal crunches.

c. A final possible factor is the fact that the men examined by Solis-Cohen were examined in the seated position, while those making up the present series were examined in the standing position.

2. *Definition of Physical Type Exhibiting Sound:* The data (table 1) indicate that the individuals exhibiting the crunch are of average physique; that is, not unusually thin nor heavy for their height. Eighty-nine per cent of

* Solis-Cohen [1] describes the sound as being occasionally diastolic, but no instances of this were observed in the present series.

TABLE I

Summary of Results

(1) Total number of personnel examined	3,224	
(2) Incidence: number of xiphosternal crunches heard	106	(3.3%)
(3) Definition of physical type:	Number of Individuals	
(a) Physique:		
Average	79	(75%)*
Heavy chest	14	(13%)
Thin chest	13	(12%)
(b) Presence of funnel chest:		
Present	26	(25%)
Absent	80	(75%)
(c) Pulse:		
70 to 90	94	(89%)
Less than 70	1	(1%)
Greater than 90	11	(10%)
(d) Blood pressure:		
(Total cases observed: 105)		
Systolic 110 to 145 and diastolic 70 to 90	76	(72%)
Systolic under 110 or diastolic under 70	23	(22%)
Systolic over 145 or diastolic over 90	6	(6%)
(e) Character of first apex sound:		
Normal	92	(87%)
Unusually loud	8	(8%)
Unusually soft	6	(6%)
(4) Description of sound:		
(a) Intensity of sound:		
Loud	25	(24%)
Medium	42	(40%)
Soft	39	(37%)
(b) Character of sound:		
Crunching or grating	62	(58%)
Spitting	41	(39%)
Clicking	3	(3%)
(c) Transmission of sound:		
Not more than one inch	87	(82%)
More than one inch to the left	19	(18%)
(d) Intensity of widely transmitted sounds:		
(Total number of sounds: 19)		
Loud	10	(53%)
Medium	8	(42%)
Soft	1	(5%)
(e) Variation of sound with respiration:		
(Total cases observed: 87)		
No variation	65	(75%)
Increase in intensity with expiration	22	(25%)

* All percentages are corrected to nearest whole number.

them have normal pulse rates, 72 per cent have normal blood pressures, and 87 per cent have apex sounds of average intensity. The only unusual physical characteristic noted among this group was the presence of some degree of funnel chest (pectus excavatum) in 25 per cent of those showing the crunch. No statistics are available on the incidence of this physical variation in its mild forms in the general population; however, Ochsner [3] found an incidence of 0.059 per cent for the severe forms among 46,705 persons. In spite of the absence of a known incidence of funnel chest in a control group of normal

persons, the very high incidence of the abnormality in those showing xiphosternal crunch in the present series indicates that there is probably a significant correlation between the two. This relationship has been mentioned before [2] as of possible causal significance and is discussed below.

3. *Description of Sound:* From the recorded results, the phenomenon under study can be described as a sound which in most cases (58 per cent) can be defined best by the words "crunching" or "grating." In a lesser percentage (39 per cent) the sound is less coarse and higher pitched, and is better indicated by the word "spitting."

For the most part (82 per cent) the sound is sharply localized just to the left and above the xiphoid and is not heard more than one inch distant from that spot. When detected over a wider area (19 per cent), the sound is more often loud than medium or soft (table 1). This latter point is in agreement with Solis-Cohen.[1]

In most cases (75 per cent), the sound does not vary with respiration, but in a small percentage of cases (25 per cent) expiration increases its intensity.

It has been assumed up to this point that the sounds described as "crunching" and "spitting" are variations of a single phenomenon. Are there any grounds to think that these two sounds represent phenomena of different origin?

To throw some light on this question, the data relative to the two sounds have been compared (table 2). Statistical analysis of the data in table 2 indicates that with the exception of intensity, transmission and variation with respiration, all of the observations show no significant differences between the two sounds. The "spitting" sound is significantly softer in intensity and less frequently widely transmitted than is the "crunching" sound; however, neither of these characteristics can be said to represent any fundamental difference between the two sounds.

Table 2 shows that an increase in intensity on expiration is seen in 39 per cent of the "spitting" sounds, and in only 16 per cent of the "crunching" sounds, which is a statistically significant difference according to the chi square method of analysis.* The most reasonable explanation of this difference is to be found in the fact noted above that the "spitting" sound is usually softer in intensity than the "crunching" sound (table 2). It is probable that a given increment of intensity would be detected more readily when the original sound is soft than when it is loud, which would account for the fact that variations in intensity were recorded more often with the softer, "spitting" sound than with the louder, "crunching" sound. It would be unwarranted to conclude from this slight difference between the two sounds that they are anything more than variations of a single phenomenon.

* The Yates formula for the calculation of chi square when the numbers involved are small [8] gave a probability value of 0.044.

TABLE II

Comparison of Data on "Spitting" and "Crunching" Sounds

	"Spitting"	"Crunching"
(1) Total number of sounds	103	
(2) Instances of the sound	41 (40%)	62 (60%)*
(3) Definition of physical type:		
(a) Physique:		
Average	31 (76%)	46 (74%)
Heavy chest	4 (10%)	9 (15%)
Thin chest	6 (15%)	7 (11%)
(b) Presence of funnel chest:		
Present	10 (24%)	16 (26%)
Absent	31 (76%)	46 (74%)
(c) Pulse:		
70 to 90	37 (90%)	54 (87%)
Less than 70	0 (0%)	1 (2%)
Greater than 90	4 (10%)	7 (11%)
(d) Blood pressure:	(40 cases)	(62 cases)
Systolic 110 to 145 and diastolic 70 to 90	30 (75%)	46 (74%)
Systolic under 110 or diastolic under 70	8 (20%)	13 (21%)
Systolic over 145 or diastolic over 90	2 (5%)	3 (5%)
(e) Character of first apex sound:		
Normal	36 (88%)	49 (79%)
Unusually loud	3 (7%)	9 (15%)
Unusually soft	2 (5%)	4 (6%)
(4) Description of sound:		
(a) Intensity of sound:		
Loud	2 (5%)	21 (34%)
Medium	13 (32%)	29 (47%)
Soft	26 (63%)	12 (19%)
(b) Transmission of sound:		
Not more than one inch	38 (93%)	47 (76%)
More than one inch to the left	3 (7%)	15 (24%)
(c) Intensity of widely transmitted sounds:	(3 cases)	(15 cases)
Loud	0 (0%)	9 (60%)
Medium	2 (67%)	6 (40%)
Soft	1 (33%)	0 (0%)
(d) Variation of sound with respiration:	(28 cases)	(55 cases)
No variation	17 (61%)	46 (84%)
Increase in intensity with expiration	11 (39%)	9 (16%)

* All percentages are corrected to nearest whole number.

POSSIBLE MECHANISM OF PRODUCTION OF SOUND

Numerous suggestions [1] have been offered in the past as to the cause of this unusual sound, including: fibrous patches on the pericardium,[4] air bubbles in the mediastinum,[5] compression of the lung by the heart thrust,[6] and movement of the xiphoid process.[7] The localization of the sound to a small, specific area would seem to dictate against fibrous patches on any serous surface, or mediastinal emphysema as possible causes. If either of these conditions was involved in its production, one would expect to hear the same sound over other portions of the precordium. The sound is not increased in intensity by inspiration as might be expected if it were due to compression of lung parenchyma by the heart thrust. The suggestion of Fishberg [7] that it is caused by movement of the xiphoid process with the cardiac impulse is the most reasonable of any of those offered.

However, even this explanation is open to criticism. The xiphoid articulates superiorly with the inferior margin of the sternum, and laterally with the cartilage of the seventh ribs. Any movement of the xiphoid would be expected to produce sounds over all of these articulations. Thus the xiphosternal crunch should be heard to the right as well as to the left of the sternum, which is not the case.

An explanation that is more consistent with the facts is: that the sound is produced by the cardiac thrust against the chest wall, leading to movement of the left seventh costal cartilage at the point of its articulation with the sternum and the xiphoid process. Several arguments support this explanation:

1. The sound is usually heard in its greatest intensity at a point directly over this articulation.

2. Funnel chest, which, as noted above, occurs commonly with the xiphosternal crunch, causes an abnormal angle between costal cartilages and the sternum. This would be expected to favor movement at the articulation between these two parts.

3. The maximal cardiac impulse is directed against the fifth, sixth and seventh ribs. Of these three, the seventh sternochondral articulation is the one most open to variation, since it includes the cartilage, sternum and xiphoid. Instances of a "loose" articulation would be more apt to occur at this point than at the other two.

4. This explanation is consistent with the previous finding of Solis-Cohen [9] that the sound is diminished or absent in the recumbent position and increased by leaning forward. These positions decrease and increase, respectively, the cardiac thrust against the chest wall, which would be expected to alter any movement at the seventh sternochondral articulation.

Summary

1. The incidence of xiphosternal crunch among 3,224 Army separatees was found to be 3.3 per cent.

2. In 58 per cent the quality of the sounds is suggested by the word "crunching"; in 39 per cent by the word "spitting."

3. These two types of sounds are probably variations of a single phenomenon.

4. Some degree of funnel chest occurred in 25 per cent of individuals exhibiting the sound. The abnormal sternochondral angle in this condition may favor production of the sound.

5. It is suggested that the sound may be caused by slight movements of the seventh costal cartilage, under the cardiac thrust, at its articulation with the sternum and xiphoid process.

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TYPHOID AND PARATYPHOID FEVER IN IMMUNIZED SUBJECTS *

By Arthur H. Rosenblum, M.D., *Chicago, Illinois*

This paper undertakes to report a series of 17 cases of typhoid and paratyphoid fever occurring in immunized army personnel on Okinawa between August and November 1945. Hodgson [1] reported a series of 84 cases of typhoid and paratyphoid fever from Lima, Peru—12 of whom had been previously immunized within three years of the onset. One of the immunized patients died. Tullis [2] reported a group of seven cases of typhoid and paratyphoid fever occurring in immunized army personnel in Sicily. Later Syverton [3] and his associates reported a series of 24 cases from Okinawa, which is stated to be the first recorded experience of typhoid in the Pacific. The cases concerned in this report apparently belonged to the same outbreak as those of Syverton, and their inclusion in the literature seemed desirable.

All of these patients were treated in a numbered general hospital on Okinawa. Many were direct admissions, while others were transfers from the various station and field hospitals. Acute febrile illnesses were prevalent at the time. The majority proved to be malaria, dengue or dengue-like fevers, infectious hepatitis, and respiratory infections. However, there remained a small group that showed protracted fever for weeks with no localizing findings. Most of the earlier cases did not appear as ill as would be expected from an inspection of their temperature charts. These cases had been called "Okinawa Fever" before their true nature became evident. By August 1945, at which time the hospital began to function, there was already evidence that these cases belonged to the typhoid and paratyphoid groups.

Because ours was the only general hospital on the island, with relatively complete laboratory facilities, we came to handle most of these cases in army personnel. Many of the patients did not run so benign a course as would be expected from preliminary reports, and there were three who were in critical condition for a good part of their hospital stay. All recovered and were evacuated.

We were initiated into this problem by our first admission to the medical service, August 5, 1945. This was a 26 year white male, with a temperature of 106°. He had one year of service with three months on Okinawa. He had completed the routine typhoid inoculations on September 23, 1944. He had been ill for three days with recurrent shaking chills, fever, and headache. There was nausea but no vomiting. Physical examination did not reveal the cause of the fever. The pulse was relatively slow and dicrotic. Repeated smears for malaria were negative. Admission white blood count was

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7300, with normal differential, and subsequently dropped to 5000. Blood cultures drawn on consecutive days were positive for *S. typhosa*. The spleen became palpable on the fourth hospital day, and rose spots appeared at the same time. Diarrhea occurred on the fifth day, and lasted 10 days. Stools became liquid but did not contain blood, pus, or mucus. Signs of bronchitis occurred on the fifth day, with numerous sibilant râles, and a respiratory rate of 40 per minute. The temperature ranged around 106° for 10 days, with repeated daily chills. Subsequently there was an irregular fall with several relapses, the entire febrile period being about one month. Blood cultures taken during the febrile relapses were positive. A stool culture on the third hospital day prior to the onset of diarrhea was positive, and was repeatedly positive afterward. The Widal test showed an initial titer to typhoid of 1/320 on August 10, increased to 1/2560 on August 17, dropped to 1/160 by September 3, and 1/80 by September 10.

This case showed some of the features of a typical typhoid: the prolonged fever, the slow dicrotic pulse, the leukopenia, the spleen, the rose spots, the bronchitis, the positive blood and stool cultures, the rising Widal titer in the third week, and the diarrhea in the second week. There were, however, many atypical features; the repeated chills, the positive blood cultures late in the disease, the abrupt rather than the step-like rise in temperature, and the rapid decline of the Widal titer after reaching a peak of 1/2560.

The occurrence of a severe typhoid in an immunized subject was an unexpected finding, and increased the suspicion that many of the atypical fevers being seen on the island were of a similar nature. Subsequent observations bore this out.

Our series of 17 cases consisted of eight typhoids, six paratyphoid A, and three that lacked laboratory confirmation. The latter ran courses so similar to those of the confirmed cases that there was little doubt as to their diagnoses. Analysis of the confirmed typhoid cases is given in table 1. Of the eight patients, five had one or more positive blood cultures. Six showed positive stool cultures, five of whom also had positive blood cultures. Two patients were diagnosed by a rising agglutination titer, having had negative blood and stool cultures. One of these developed a titer of 1/640, and the other 1/320.

Analysis of the confirmed paratyphoid A cases is indicated in table 2. Five of the six patients had positive blood cultures. Two showed positive stool cultures as well as positive blood cultures. One was diagnosed on the basis of a rising agglutination titer which reached a peak of 1/1280.

The three cases lacking laboratory confirmation were not seen in the initial phases, and it is probable that positive laboratory evidence could have been obtained had they been seen early. Their clinical course was essentially that of the proved paratyphoids.

Immunization Records. All patients had primary or stimulating injection of triple typhoid vaccine within a year. This would be expected as immunization procedures on soldiers serving overseas had been rigidly enforced.

TABLE I

Typhoid Fever Cases

Case	Blood Culture	Stool Culture	Highest Agglutination Titer	Highest Temperature	Duration Fever, Days
1	Pos.	Pos.	1/1280	105	26
2	Pos.	Pos.	1/2560	106	32
3	Neg.	Pos.	1/160	102	23
4	Neg.	Neg.	1/640	104.2	47
5	Pos.	Pos	1/80	105	60
6	Pos.	Pos.	1/320	107	55
7	Neg.	Neg.	1/320	104.8	32
8	Pos.	Pos.	Neg.	104	25
Total 8	5 Pos. 3 Neg.	6 Pos. 2 Neg.			Average Duration 38 days

Clinical Features. The essential clinical features are tabulated in table 4. The typical clinical course was that of sudden onset with high fever, repeated chills, and anorexia. In general the symptomatology was similar in typhoid and paratyphoid A, with the typhoid patients usually being sicker. The three critically ill patients were confirmed typhoids.

The duration and height of the fever are indicated in tables 1, 2, and 3. In all but one the disease was ushered in by a marked hyperpyrexia, usually of 104° to 106°. One typhoid patient exhibited a temperature of 107° early in the disease. Only one patient, a confirmed paratyphoid, developed the usually described step-like rise in temperature. Four of the typhoid patients developed febrile relapses after it had seemed that they were convalescent.

Of the 16 patients having chills, 14 had recurrent chills. Gastrointestinal symptoms, anorexia, nausea, vomiting, abdominal pain, and diarrhea were common. Diarrhea when it occurred typically made its appearance in the second week, lasting one to 14 days. In a few cases diarrhea occurred in the first week. The typical diarrheal stools were watery, but did not contain blood, pus, or mucus. Diarrhea was absent in seven cases.

TABLE II

Paratyphoid A Cases

Case	Blood Culture	Stool Culture	Highest Agglutination Titer	Highest Temperature	Duration Fever, Days
9	Neg.	Neg.	1/1280	104	37
10	Pos.	Pos.	1/1280	102.2	30
11	Pos.	Neg.	1/640	105.6	20
12	Pos.	Pos.	1/320	105	30
13	Pos.	Neg.	1/320	105.2	35
14	Pos.	Neg.	1/40	104.8	35
Total 6	5 Pos. 1 Neg.	2 Pos. 4 Neg.			Average Duration 31 days

TABLE III

Duration of Fever and Highest Temperature
Unconfirmed Cases

Case	Highest Temperature	Duration Fever, Days
15	104	20
16	105	30
17	101.2	20
Average Duration		23 days

All patients showed a bradycardia at the onset, with a dicrotic pulse usually present. Three typhoid patients exhibited a tachycardia in the second and third weeks. Two of these had pneumonitis, and the third severe intestinal hemorrhages.

Ten cases had a palpable spleen. This was often not felt on admission, but could usually be palpated toward the end of the first week. It was soft, tender, not so well defined, and more difficult to palpate than the firm spleen of malaria.

TABLE IV

Symptomatology

	Brady-cardia	Abrupt Onset	Ano-rexia	Chills	Pal-pable Spleen	Head-ache	Diar-rhea	Ab-dominal Pain	Vomit-ing	Rose Spots	Pal-pable Liver
Typhoid	8	8	8	8	6	7	4	3	2	3	1
Para A	6	5	6	5	3	2	4	2	1	1	0
Unconfirmed	3	3	3	3	1	3	2	1	1	0	0

Three patients showed a tender palpable liver. Rose spots were observed in only four patients, three typhoids, and one paratyphoid. The rash was observed in the second and third weeks rather than the first. In all four, there was evidence of active septicemia with positive blood cultures at the time the rash occurred.

Laboratory Studies. All patients except one showed a leukopenia at the onset or shortly thereafter, and the leukopenia persisted throughout the disease. One paratyphoid A showed a leukocytosis of 16,050 at the onset, and a prompt drop to normal in four days.

Blood cultures were positive in 10 patients, five typhoids, and five paratyphoids. In most of these the cultures were repeatedly positive not only in the first week but well into the second and third weeks. Positive cultures were frequently obtained if the patient were having chills and fever regardless of the duration of the disease. In several instances positive blood cultures were obtained during a febrile relapse, after the patient had apparently been over the acute stages of the disease.

Stool cultures were positive in eight cases, six typhoids, and two paratyphoid A. One of these, a confirmed typhoid, had no diarrhea, but was constipated. Another showed a positive typhoid culture in the first week

several days prior to the onset of diarrhea. The rest showed positive cultures well into the second and third weeks, and were usually repeatedly positive.

The agglutination titers are tabulated in table 5. The data are of necessity incomplete. Many of the patients did not come under observation until late in the disease. Others were evacuated soon after the diagnosis was established, thus shortening the period of observation. Finally a shortage of typing sera prevented us from carrying out as many studies as we would have wished to. The titers at various stages of the disease were of interest, but did not follow a regular pattern. Many confirmed cases of typhoid and paratyphoid A showed no significant rise at all. Some showed a rise in titer that was sustained throughout the period of observation. Others showed a rise followed shortly afterward by a fall. Of two critically ill typhoid patients, having repeatedly positive blood cultures, one showed a maximum titer of only 1/80, and the other 1/320, during eight weeks' observation. It is apparent that the agglutination titer, unless definitely positive had no

TABLE V

Agglutination Titer for the H Antigen of *Salmonella typhosa*, *Salmonella paratyphi A*, and *Salmonella paratyphi B*

Case	Antigen	Week of Illness						
		1	2	3	4	5	6	7
1	T		1/320		1/320	1/320	1/1280	
	A		0					
	B		0					
2	T		1/320	1/2560		1/160	1/80	
	A		1/80					
	B		1/20					
3	T				0	1/160		
	A				1/80	1/160		
	B				0	1/80		
4	T			0	1/320	1/640	1/320	
	A			0	0	1/320	1/160	
	B			0	0	1/80	1/80	
5	T		0	1/80	0	0	0	0
	A		0					
	B		0					
6	T		0		0		1/320	
	A		0					
	B		1/80					
7	T			1/320	1/320	1/320	1/160	
	A			1/160	1/160	1/80	1/80	
	B			1/160	1/160	1/320	1/160	
8	T			0	0	0		
	A			0	0	0		
	B			0	0	0		

TABLE V—*Continued*

Case	Antigen	Week of Illness						
		1	2	3	4	5	6	7
9	T	1/40			1/40	1/40		
	A	1/80			1/160	1/1280		
	B	1/20			1/20	1/20		
10	T		0					
	A		1/1280					
	B		0					
11	T	0		0				
	A	0		1/640				
	B	0		0				
12	T		0					
	A		1/320					
	B		0					
13	T	0	0	0				
	A	0	1/40	0	1/160	1/160	1/320	
	B	0	0	0				
14	T			0				
	A		1/40	0	0	0		
	B			0				
15	T	1/40		1/40		1/40		
	A	1/40		1/80		1/40		
	B	0		0		0		
16	T		1/80			0	0	0
	A		1/20			1/160	1/80	0
	B		0			0	1/80	0
17	T		1/160	1/160				
	A		1/160	1/160				
	B		0	0				

diagnostic value, and that unless it were repeated frequently, a rising titer might be missed. It was felt that a rising titer was of more importance than an isolated determination. The fact that all these patients had recently received triple typhoid immunizations would throw doubt on the significance of slight elevations in titer.

Differential Diagnosis. These cases had to be differentiated from other acute infectious diseases, especially those previously listed. Malaria showed many similar features; the leukopenia, the repeated chills, the spleen, and the absence of other localizing findings. However, a diagnosis in malaria could usually be made by careful blood smears, and in doubtful cases a therapeutic test settled the issue. The dengue-like fevers were confusing but fortunately ran a self-limited course of four to seven days. Acute hepatitis showed similar symptoms in the early febrile stage, but the appearance of icterus after the fourth or fifth day revealed the diagnosis. Some of the dysenteries showed

an acute onset with chills and fever. However, the subsequent occurrence of typical dysentery stools, with positive bacteriologic cultures established the diagnosis.

Treatment. The treatment of these patients was entirely supportive and symptomatic. It consisted of maintaining nutrition and hydration, and the recognition and treatment of complications. The seriously ill patients were given special nursing care. Intravenous fluids were used in a few cases, but were given cautiously, because of the myocardial weakness that these patients often develop. The two patients who developed pulmonary complications were given oxygen. Transfusions were used on two patients, one of whom had massive intestinal hemorrhages. The latter had 21 transfusions in all. Blood was drawn from recently immunized donors whenever possible. Sulfa drugs and penicillin were used on a few of the patients, with no beneficial effects. The patients having pulmonary complications were given such therapy in an effort to prevent secondary infection. Although secondary infection did not occur, there was no improvement that could be attributed to chemotherapy. It would have been of importance to try streptomycin, but none could be obtained.

Sequelae. Two patients developed pneumonitis, early in their illness. One showed definite evidence of myocardial weakness, but facilities were not available at that time for electrocardiographic studies. One had numerous massive intestinal hemorrhages. All suffered from moderate to marked weakness and general debility, and many lost considerable weight in spite of our efforts to support them with a nutritious diet and vitamins. Most of them developed a mild secondary anemia. It was felt that their convalescence would be facilitated by better dietary and living conditions, and hence all were evacuated as soon as they had recovered from the acute stage of their illness.

Epidemiology. No conclusions could be drawn regarding epidemiology. With the exception of two cases from the same organization, all came from various outfits widely distributed on the island, both service and combat. One patient, a typhoid, became ill en route from Luzon. Most of the active combat was over by August 5. None of the patients admitted eating or drinking anything but approved army food and water. The infection could not be attributed to the eating of raw vegetables, though the unreliability of histories must be admitted.

It was learned from the natives that the milder syndrome of "Okinawa Fever" was known to them, and that typhoid and paratyphoid were probably endemic. It may be surmised that some individuals do not develop as high degree of immunity as others to the standard typhoid immunizations, and that if the exposure is heavy enough, infection may occur. When one considers the large number of troops involved, and the relatively small number of clinical cases, it is apparent that the control of this disease is highly effective.

ADDITIONAL CASE REPORTS

Case 2. A 24 year white male had sudden onset of headache, joint pains, backache, general malaise, and chills on August 20, 1945. He remained on duty for five days, but the occurrence of severe diarrhea, nausea, and vomiting forced him to sick call. After hospitalization at a field hospital for five days, where the above symptoms persisted, he was transferred to us on the tenth day of his illness. Admission examination showed a toxic, acutely ill patient, having a temperature of 105°, with a heart rate of 100. The radial pulse was dicrotic. The outstanding symptom was severe continuous diarrhea, the stools containing mucus, but no pus or blood. Proctoscopic examination gave normal findings. Admission blood and stool cultures were positive for *S. typhosa.* The patient showed a high sustained fever for the first week.

On September 6, the seventeenth day of the illness, rose spots appeared, and the spleen became palpable. Sibilant râles were heard in the chest at this time. On September 7, he had a massive intestinal hemorrhage, filling a bed pan with almost pure blood. At the same time, the temperature dropped to normal, and the pulse rate increased. The temperature curve subsequently showed a septic response, continuing irregularly with peaks of 104° to 105°. The total febrile period was about 60 days. The pulse rate during this time was irregularly rapid.

For the next 20 days, the patient had repeated massive bowel hemorrhages. On several occasions he went into shock, becoming almost pulseless, with blood pressure readings below 80 systolic. He was supported by repeated transfusions of whole blood, receiving a total of 21 transfusions, for 10,700 c.c. blood. In one 24 hour period, he received 2000 c.c. blood. During all this time he continued to have a high irregular fever.

The admission white count was 9400, hemoglobin 80 per cent, and red count 4,500,000. The white count dropped to 4600 on September 7. The red count fell to a low of 2,030,000 with 6 grams hemoglobin on October 1. The admission urine specimen showed one plus albumin, and 25 red cells per high power field. Repeated agglutination studies did not show any increased titer to typhoid or paratyphoid organisms. After the last hemorrhage on September 23, the patient made a gradual recovery, and by the middle of October had a normal temperature. He was evacuated at this time. It was subsequently learned that he had a relapse in Manila lasting about a week, with a temperature up to 102°.

Case 3. A 26 year white male became ill August 18, 1945, with fever, low back pain, and pain in the legs. He also complained of diarrhea, anorexia, and a feeling of fullness in the abdomen. He was hospitalized in a field hospital for 12 days where he was observed to have a high fever, repeated chills, and low back pain. He was transferred to us on the thirteenth day of his illness.

On admission, the patient appeared critically ill. Admission temperature was 105.4°, with a pulse rate of only 100 per minute. The radial pulse was of poor quality and dicrotic. The liver was palpable one centimeter below the costal border, and the spleen was just palpable. The abdomen was moderately distended. There was a soft systolic apical murmur. Diarrhea was present for the first three days of his hospital stay. On the second hospital day, he had a severe chill and a fever of 107°. For the following 10 days, his condition remained critical. The pulse became as rapid as 140 per minute, and respirations 60 per minute. The chest showed numerous râles over the right lower lobe, and a few on the left. Pulse became weak and thready, and the heart tone of poor quality. Admission blood and stool cultures were positive for *S. typhosa.* It was felt that this patient had toxic myocarditis and bronchopneumonia, complicating his typhoid fever.

He was supported with oxygen. Penicillin was given for the prevention of secondary infection. It was not felt that penicillin had any beneficial influence, but at least there was no spread of the pneumonia. Intravenous fluids were used cautiously; on

September 4, he was given 250 c.c. blood from a recently immunized donor. On September 6, the nineteenth day of the disease, numerous rose spots appeared on the chest and abdomen. They remained for five days. The patient subsequently showed steady improvement, so that by September 15, one month after the onset, he appeared to be convalescent. However, after a normal temperature for one week, he showed a relapse. He had a typical step-like rise of temperature, reaching 105° on the sixth day. However, he did not become seriously ill during the relapse, and after a step-like fall became normal on the fifteenth day.

The white count on admission was 3350. Agglutination studies were negative on September 3 and September 27. There was a rise in the titer against typhoid to 1/320, on October 5, 1945. Blood cultures were repeatedly positive in various stages of the disease, including one drawn during the relapse. A moderate secondary anemia was apparent by September 18; red count 2,940,000, with 60 per cent hemoglobin.

Case 4. A 32 year white male was admitted on August 11, 1945. He became ill en route from Luzon aboard an L.S.T. He stated that he had been sea sick for eight days, and had a chill and high fever the night preceding admission. The morning of admission he had another chill, followed by high fever and profuse sweating. He vomited once the day of admission. He had 34 months service, with 21 months in the tropics.

On admission he had a fever of 104° with a relatively slow dicrotic pulse. The spleen was palpable and tender. There was slight liver tenderness. There was no rash. In spite of his high fever, he did not appear seriously ill.

Admission blood culture was positive for *S. typhosa*. Repeated stool cultures were likewise. The temperature curve was septic in type, with peaks of 104° to 106°, and subnormal depressions. The total duration of the fever was only 19 days, and there was no relapse.

The white count on admission was 4200. The Widal test August 15 showed a titer to typhoid 1/320. On September 1, it was the same. On September 20, it rose to 1/1280.

Case 5. A 28 year negro was transferred to us on August 28, 1945 for observation for leukopenia associated with vague complaints of chest pain, headache, and leg pains. He showed a white count of 2100, with 70 per cent lymphocytes. He had no fever until the fourth hospital day, when he started having a steplike rise in temperature, reaching a peak of 105.6° on September 7. He had one shaking chill on September 6. Subsequently the temperature assumed a more septic character, and after September 15, there was a step-like fall. The total duration of the fever was three weeks. The pulse was relatively slow and dicrotic throughout. He developed some liver tenderness, and a distended abdomen. At no time did he appear seriously ill.

The blood culture September 6 was positive for paratyphoid A. Agglutination studies were negative on August 30. On September 27, the titer to paratyphoid A rose to 1/640. He made an uneventful recovery.

Case 6. A 29 year old negro was admitted October 14, 1945. He had 20 months service, 11 months overseas. He arrived on Okinawa September 13, 1945 from the European theater. He became ill October 10 with recurrent shaking chills and high fever. On admission he complained of severe headache, retro-orbital pain, and general malaise. He also had some cough, mild abdominal cramps, nausea, and anorexia.

Physical examination on admission showed a fever of 105°, bradycardia, and dicrotic pulse. The spleen and liver were not palpated. There was an irregular fever, with a gradual downward trend, lasting about one month. At no time did he appear seriously ill.

Blood culture drawn on admission was positive for paratyphoid A. Agglutination

studies on October 16 showed a titer to paratyphoid A to 1/40, November 1, 1/160, and November 9, 1/320. Admission white count was 5200. There was no diarrhea. He made an uneventful recovery.

Summary

1. A report is made of 17 cases of typhoid and paratyphoid fever in military personnel on Okinawa.

2. All patients had primary or stimulating immunizations within one year.

3. Diagnosis was based principally on positive blood and stool cultures, and in a few instances on rising agglutination titers. Three cases were unconfirmed by the laboratory.

4. Agglutination studies showed no constant pattern. Some of the sicker patients showed little or no rise in titer. Others showed a significant increase in titer, followed by a fall, while still others showed a sustained increase.

5. These patients were characterized by many atypical features. The sicker patients showed a marked tendency to relapse.

6. The cases occurred in outfits widely scattered on the island, both service and combat.

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PROLAPSED GASTRIC MUCOSA: A POSSIBLE CAUSE OF "GASTRIC" SYMPTOMS IN RIGHT HEART FAILURE *

By MYRON MELAMED,† M.D., *New York, N. Y.*, and ABRAHAM MELAMED,‡ M.D., *Milwaukee, Wisconsin*

IT has been definitely established that prolapse of the gastric mucosa into the duodenum is capable of producing symptoms. The clinical signs and symptoms are usually not severe, unless complications develop, but they are of sufficient severity for such patients frequently to seek medical advice. The diagnosis of prolapsed gastric mucosa can only be established by roentgen means. Clinically the condition might be suspected when "atypical peptic ulcer" symptoms are present.

Many theories have been advanced to explain the etiology of prolapsed gastric mucosa but one of the more logical explanations can be found during postmortem examinations of patients who have succumbed to congestive heart failure. It is well known that in such states there are markedly redundant, edematous and mobile gastric rugae and edema of the submucosa. As a result of such postmortem observations, we wish to propose that such conditions provide an adequate basis for increased mobility of the gastric mucosa and subsequent prolapse into the duodenum, and that in many cases of congestive heart failure "gastric" symptoms are due to such an abnormality.

This report is mainly concerned with the observations made in two cases studied at autopsy and in two others in whom the clinical states are similar. Roentgenographic and pathologic evidence was obtained in case 1. In case 2 no roentgen studies were performed, but the anatomic findings were so pronounced that one could not reasonably doubt that prolapse of the mucosa had occurred in vivo. Two cases (numbers 3 and 4), comprising the second group, were not confirmed anatomically. The clinical signs and symptoms in both cases are consistent with a diagnosis of right heart failure; the "gastric" symptoms can be explained on the basis of herniation or "intussusception" of the mucosa into the duodenum.

CASE REPORTS

Case 1. History. A 56 year old white male entered Mount Sinai Hospital, Chicago, on January 1, 1947 with abdominal pain of three months' duration and vomiting for three weeks. In October 1946, the patient noted sudden onset of dyspnea, weakness and profuse perspiration associated with a "pressure" sensation in the left upper

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From the Department of Pathology, Mount Sinai Hospital, Chicago, Illinois and Department of Radiology, Evangelical Deaconess Hospital, Milwaukee, Wisconsin.

† Formerly resident, Department of Pathology, Mount Sinai Hospital, Chicago, Illinois; Resident, Department of Radiology, Mount Sinai Hospital, New York, N. Y.

‡ Director, Department of Radiology, Evangelical Deaconess Hospital, Milwaukee, Wisconsin.

quadrant of the abdomen. He was confined to bed for one week under a physician's supervision, following which episodes of vomiting associated with epigastric pain occurred after meals for four days. After four days the vomiting subsided while the patient was on a "light" diet but the pain persisted and the patient complained of "indigestion." Two to three weeks prior to entrance to the hospital, the patient experienced epigastric pain three to four hours after meals, relieved by drinking milk. The patient lost 36 pounds in three months.

Physical Examination. Cyanosis of the lips was noted. The blood pressure was 100 mm. mercury systolic and 74 mm. mercury diastolic, pulse rate 64/min. and regular, temperature 98.6° F., respiratory rate 24/min. Systolic murmurs were heard at all the valve areas, the aortic murmur being harsh in character. The liver was palpable two fingers below the costal margin. An old appendectomy scar was present in the right lower quadrant.

Laboratory Data. The red count was 4,500,000 per cu. mm.; white count, 9,900 with an essentially normal differential; hemoglobin, 13.5 gm. Urinalysis yielded essentially normal results. The stools were negative for blood. The blood chemistry determinations were as follows: sugar 110 mg. per 100 c.c. of blood, urea 12.2 mg. Gastric analyses on fasting and Ewald meal specimens were unsatisfactory for titration inasmuch as only small amounts of mucoid material could be obtained. Electrocardiographic examination on January 7, 1947 revealed changes compatible with an old anterior wall infarction. Roentgen studies of the upper gastrointestinal tract on January 8, 1947 revealed no changes in the esophagus. The mucosal pattern of the stomach was exaggerated and at times the prepyloric mucosa was seen to prolapse slightly into the duodenum (figure 1). Gastric motility was not delayed.

Course. The temperature remained normal throughout the hospital stay. On

FIG. 1. "Spot" roentgenogram of distal stomach and duodenal bulb shows indentation of the base of the duodenal bulb. Rugal markings extend into the duodenal bulb in radial fashion from the prepyloric region. The duodenal bulb is not deformed.

peptic ulcer management and bed rest the patient improved and was discharged on January 15, 1947.

The patient was readmitted to the hospital on February 10, 1947 with a recurrence of the epigastric and hypogastric pain of six days' duration and vomiting for three or four days. Cyanosis of the lips and fingers was present. The blood pressure was 100/90, pulse 100/min., respirations 24/min. There was epigastric tenderness but otherwise the physical findings were essentially the same as on previous examination. On February 12, 1947, there was sudden onset of precordial pain, dyspnea and marked cyanosis. Bilateral basal râles were heard and bilateral pleural effusions were noted. Laboratory results were non-contributory. The patient died on February 14, 1947 after a progressive downward course. No digitalis therapy was employed at any time during the patient's hospitalizations. Autopsy examination was performed by Dr. I. Davidsohn.

Autopsy Findings. The body was that of a well developed, fairly well nourished white male; the skin was pale. Cyanosis of the lips was present. The heart was considerably enlarged mainly as a result of extreme dilatation and to a lesser degree due to thickening of the ventricular walls. It weighed 460 gm. The left ventricular wall measured 15 mm., the right ventricular wall 6 mm. The apex was formed by the left ventricle and the heart had a globular shape. Other findings were calcareous aortic stenosis; old fibroplastic rheumatic deformity of the mitral valve; recent thrombotic occlusion of the anterior descending branch of the left coronary artery; sclerosis of all coronary branches; myocardial infarction of the left anterior wall and anterior inter-ventricular septum; old healed scars, left ventricle; old and recent pericarditis; atherosclerosis of the aorta.

The lungs exhibited signs of acute edema and chronic passive congestion. The right lung weighed 1,000 gm. and the left 850 gm. Pleural adhesions, bilateral hydrothorax and ascites were also found. A right lower quadrant old appendectomy scar was present. The liver which weighed 1,560 gm. showed chronic passive congestion. The spleen weighed 220 gm. and showed cyanotic induration. The stomach possessed edematous and redundant rugal folds. Evidence of acute and chronic passive congestion was also present.

Cause of Death. Myocardial infarction.

Comment. Arteriosclerotic heart disease was responsible for congestive heart failure. The latter state gave rise to edema and redundancy of the prepyloric gastric rugae, terminating in prolapse distally. The upper abdominal symptoms and "indigestion" were evidently the result of the prolapsing mucosa into the duodenum.

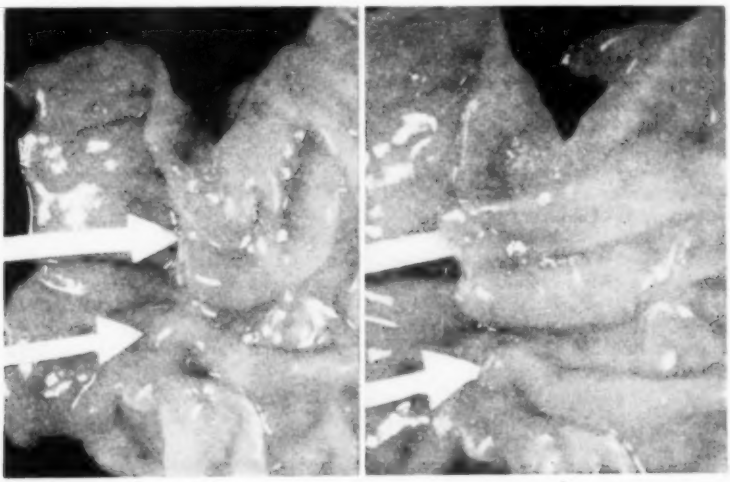
Case 2. History. A 75 year old white male was admitted to Mount Sinai Hospital, Chicago on June 28, 1947 with severe asthma, the latest episode of three weeks' duration. For three weeks there had been increasing dyspnea and orthopnea and mild ankle swelling. Anorexia had been quite marked. The patient had been an "asthmatic" for many years.

Physical Examination. Cyanosis of the lips and fingers was present and the patient was quite dyspneic. The temperature was 99.6° F., respirations 22/min., pulse 88/min. and irregular. The chest was barrel-shaped and hyperresonant bilaterally. Wheezing was diffuse and symmetrical. A systolic murmur was heard over the entire precordium and auricular fibrillation was present. The liver was palpated three fingers below the costal margin but the spleen was not clinically enlarged. No ascites was found. Moderate pitting edema of the legs was noted. The clinical impression was cor pulmonale syndrome with chronic emphysema and auricular fibrillation.

Course. The patient died on June 30, 1947, 36 hours after admission, following a

progressive downward course and a rise in temperature to 102° F. No laboratory data are available in this case but autopsy was performed two and one-half hours after death by Dr. I. Davidsohn.

Autopsy Findings. The body was that of an elderly, fairly well nourished white male. Pitting edema of the legs was elicited and considerable cyanosis was visible. The external appearance of the chest was typical of the emphysematous type. The heart weighed 360 gm. The right ventricular wall measured 6 mm. thick, the left ventricular wall 12 mm. The right ventricular chamber was enlarged, the wall thickened and eccentric hypertrophy of the right ventricle was noted. The pectinate muscles of the right ventricle were thick and widened. In addition, there were calcifications and atheromatosis of the mitral ring, mild healed endocarditis of the aortic valve with atheromatosis, and mild coronary sclerosis.



a *b*

FIG. 2, *a*. Photograph of pyloroduodenal junction at postmortem examination. The points of the arrows denote the location of the pyloric ring. Redundant, edematous, and giant gastric rugae are seen proximal to the arrow heads or duodenum.

FIG. 2, *b*. Obscuration of the upper arrow head by the redundant rugae indicates prolapse of the gastric mucosa. The prepyloric gastric folds were easily swayed manually distally or proximally.

Both lungs were congested. The left lung weighed 480 gm. and the right weighed 580 gm. Chronic emphysematous changes were obvious. Apical scars with bronchiectasis and bullous emphysema were also present. A purulent bronchitis was also seen. Old pleural adhesions were found.

The liver showed evidence of acute passive congestion and edema, weighing 1,680 gm. The gall-bladder was edematous. The spleen weighed 190 gm. and showed cyanotic induration. Cortical hyperplasia of the adrenals was noted. The pancreas showed evidence of lipomatosis. Arterio- and arteriolosclerosis of the kidneys, which weighed together 370 gm., was noted; a few congenital cysts were also observed. The urinary bladder displayed evidence of inflammation of the wall.

The esophagus showed no change but the rugae of the distal one-half of the stomach, especially in the prepyloric area, were thickened, hemorrhagic and pendulous. The prepyloric mucosal folds were herniated into the duodenum. They were so redundant that they could be swung from the gastric side to the duodenal side and vice versa (figure 2, a and b). Figure 3a represents a longitudinal section of the pylorus and the proximal portion of the duodenum (A). The fold is made up entirely of gastric mucosa (B). The duodenal elements begin to appear at the lower junction between the fold and the wall (C). The surfaces are covered with thick mucus. The superficial layer of the mucosa is densely infiltrated with plasma cells. The capillaries are widely distended with red cells (figure 3, b), in some places forming papillary projections. The congestion of the surface interferes with the emptying of the glands which are dilated and filled with mucus (figure 3, c). The duodenum was deformed as the result of a healed peptic ulcer. Diverticulosis of the colon was observed. The scrotum was edematous and fluid was found in the abdominal cavity.

Cause of Death. Chronic emphysema, cor pulmonale and chronic bronchitis.

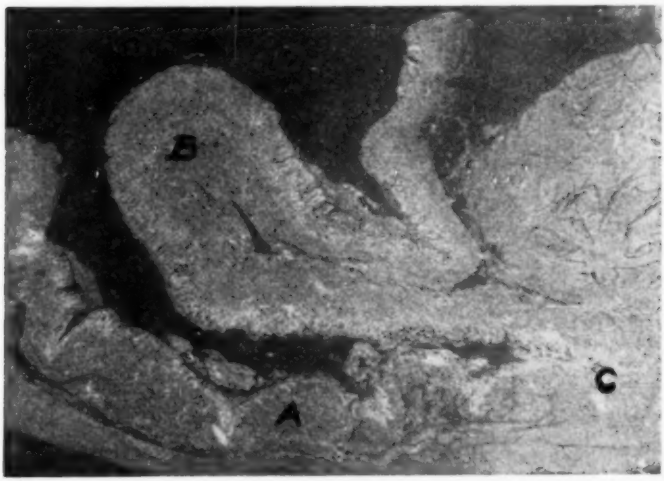


FIG. 3, *a*. Photograph of glass slide containing section of prolapsing or herniating gastric rugal fold. The gastric fold (B) lies above the inferior wall of the duodenum (A). The pyloroduodenal junction is represented by the letter C.

Comment. In this patient chronic asthma and pulmonary fibrosis accounted for the cor pulmonale syndrome. The right heart failure led to a "congestive gastritis," prolapse of the redundant prepyloric folds and "anorexia." The gastrointestinal complaints were not noted in detail on the hospital record.

Case 3. History. A white male aged 64 years, first became ill during the latter part of 1946 and first consulted a physician in October 1946. In December 1946 the patient developed pain in the chest. During a four month period, the patient lost 20 pounds in weight and complained of fullness in the epigastric region and slight dys-

phagia, relieved by baking soda. The patient stated that a "positive blood test" was discovered and he subsequently received many injections for this condition.

Roentgen studies of the gastrointestinal tract of this ambulatory patient on April 15, 1947 revealed the following: Preliminary fluoroscopy of the chest revealed an area of increased density in the left lower chest adjacent to the cardiac shadow which was due to interlobar pleural thickening and/or fluid. A tumor in the underlying lung could not be ruled out. The heart was slightly enlarged. The esophagus exhibited no intrinsic pathology when opacified with the opaque substance. The mucosal pattern of the stomach was very prominent and exaggerated in the prepyloric area; polypoid changes were simulated or actually present. Gastric peristalsis and distensibility were complete. Serial studies of the distal stomach and duodenum disclosed filling defects in the base of the bulb which were typical of prolapse of the gastric mucosa (figure 4, a). The six hour roentgenogram showed no retention in the stomach; this film revealed enlargement of the liver, a tongue-like projection extending down almost to the level of the iliac crest. The lower border of the spleen was located at the level of the left costal margin. Barium enema studies revealed no intrinsic pathologic changes in the colon.

A blood Wassermann test performed October 28, 1946 was reported as 3 plus by the Wisconsin State Laboratory. Penicillin therapy was administered between No-

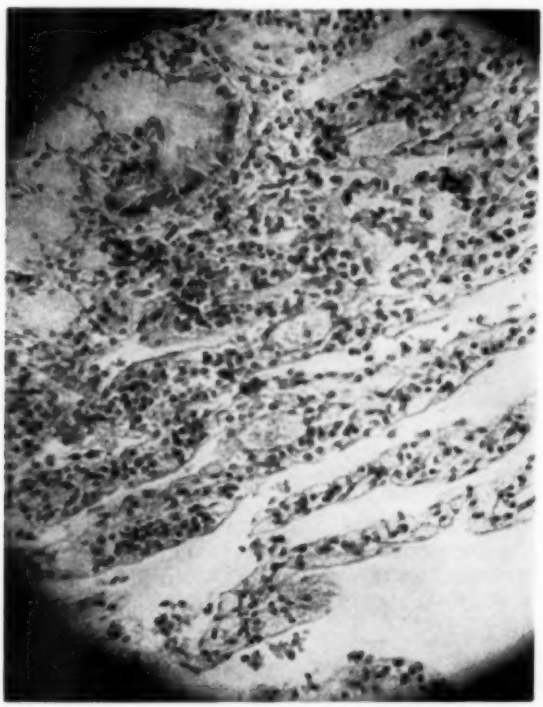


FIG. 3, *b*. High power photomicrograph of section through the redundant portion of the gastric mucosa showing widely distended capillaries filled with red blood cells.

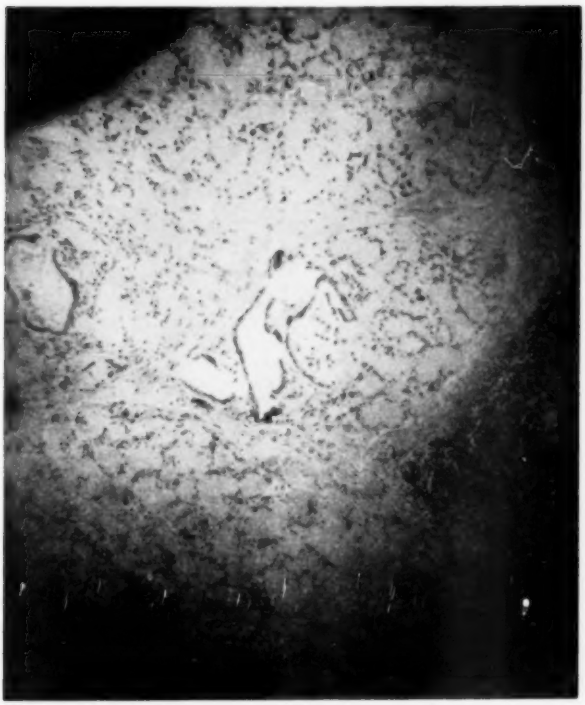


FIG. 3, *c*. Low power photomicrograph of mucosa near pyloroduodenal junction discloses a few dilated gastric glands containing mucus.

vember 3 and 18, 1946. Bismuth and mapharsen therapy was used November 27, 1946 to February 19, 1947. In April 1947 the blood Wassermann became negative but in August 1947, the test was reported as 4 plus. Numerous sedimentation rate determinations were done; the rate decreased from 8–30–69–76 on March 17, 1947 to 2–6–18–27 on August 1, 1947. Urinalysis on October 28, 1946 revealed no albumin or sugar but on February 28, 1947 a slight trace of albumin was found. On November 1, 1946 the tuberculin patch test was reported as 1 plus.

Follow-up Notes. The patient returned for roentgenographic studies of the upper gastrointestinal tract and chest on August 13, 1947. In the interval, however, the patient had experienced two "heart attacks" which confined him to bed most of the time. During these episodes auricular fibrillation was noted. Rather severe episodes of decompensation were combated with digitalis treatment but his cardiac status remained poor. His main complaint was dyspnea. The cardiac rhythm became regular but the rate remained rapid. Heart tones were rather distant and a very soft apical murmur could be heard. Gross pulsations of the lower left chest were visible. The blood pressure readings were 140/80 in the right arm and 115/82 in the left arm. Two plus ankle edema was noted. Electrocardiographic studies on August 11, 1947 showed changes either due to digitalis effect or left ventricular strain without axis shift.

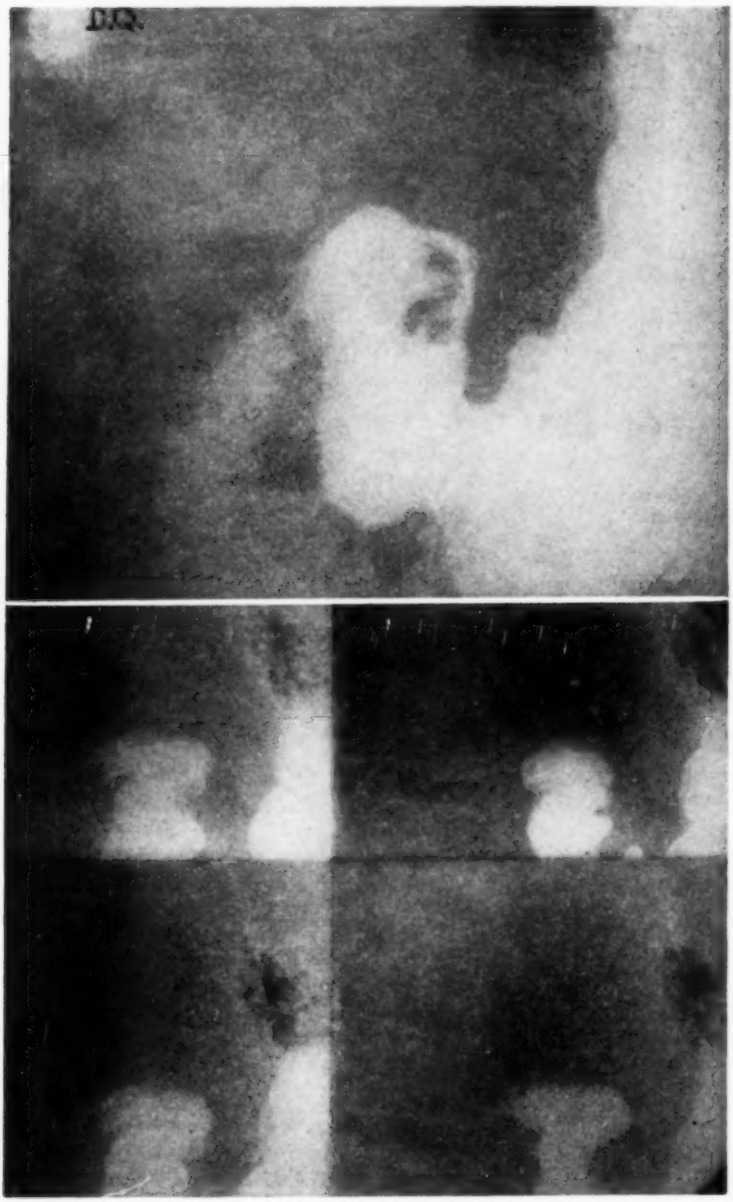


FIG. 4, *above*. Roentgenogram of distal stomach and duodenum (April 15, 1947) shows filling defect in midst of proximal duodenum due to prolapsing gastric mucosa.

FIG. 4, *below*. Serial views (Aug. 11, 1947) show no evidence of prolapse on the gastric mucosa. The increased mobility of the gastric rugae originally noted on April 15, 1947 is no longer present or demonstrable.

A teleroentgenogram of the chest (August 13, 1947) revealed a moderate pleural effusion on the left side. The condition of the underlying lung was not ascertained. Pleural thickening was present in the right costophrenic angle. The heart seemed to be slightly enlarged to the left but the left cardiac border was partially obscured by the fluid in the chest. Slight dilatation of the aorta was evidently present.

Opacification of the esophagus yielded no evidence of obstruction. The mucosal pattern of the stomach was exaggerated throughout. No prolapse was present. Clinically, though, the patient complained of dysphagia. No retention studies were performed due to the physical condition of the patient.

We have been informed that this patient died October 13, 1947 at the Milwaukee County General Hospital. The description of the postmortem findings by Dr. J. M. Kuzma, Director of Laboratories, is as follows: "The patient had a small cell bronchiogenic carcinoma arising from the principal bronchus of the left lower lobe. This tumor had metastasized to the thoracic and abdominal lymph nodes, the liver and right adrenal. In addition to this, he had a golf ball sized infiltrating tumor involving the head of the pancreas. This was firmly attached to the duodenum but the common duct was in the superficial part of the tumor and not occluded. This tumor was primary in the pancreas and was an adenocarcinoma in sharp contrast to the small cell carcinoma of the lung. No metastases of this tumor were found. He also had multiple pedunculated polypi of the descending and sigmoid portions of the colon.

"Incidental findings were right lower lobe bronchopneumonia, a bifid pelvis of the right kidney and benign prostatic hypertrophy. There was chronic passive congestion of the liver and spleen. The heart weighed 330 gm. and was brown and flabby. No anatomic evidence of prolapse of the gastric mucosa was found."

Comment. Notwithstanding the postmortem findings, we believe that right heart failure was responsible for the herniation of the gastric mucosa in this patient with serologic evidence of syphilis. When the patient was examined roentgenologically for the first time in April 1947 there were undeniable clinical and physical signs of congestive heart failure. Roentgen examination revealed prolapse at this time. Shortly thereafter, an acute episode of cardiac decompensation and auricular fibrillation ensued. After two to three months of intensive symptomatic treatment, his cardiac status was considerably improved. The second roentgen examination of the stomach and duodenum on August 13, 1947 was performed in such a clinical state. At this time, the prolapse was almost indiscernible (figure 4, b). The progressive downward course, however, was due to malignant lesions in the lungs and pancreas with metastases to other sites, the patient ultimately succumbing to his cachectic state and heart failure with pulmonary edema. The examiner found no prolapse but the status of the gastric mucosa was not noted in detail.

This case demonstrates that prolapse can be reversible and can disappear with subsidence of edema and congestion and clinical improvement of the patient. Thus, early amelioration of gastric symptoms under treatment can indicate a favorable response to therapy.

Case 4. History. A male patient, aged 58, was referred as an outpatient for roentgen examination of the gastrointestinal tract and gall-bladder on January 18, 1946. The patient stated that he suffered from "heart trouble" and that two weeks previously he had vomited a cupful of blood. He had lost no weight but complained of indefinite upper abdominal discomfort. There was no relationship of symptoms to

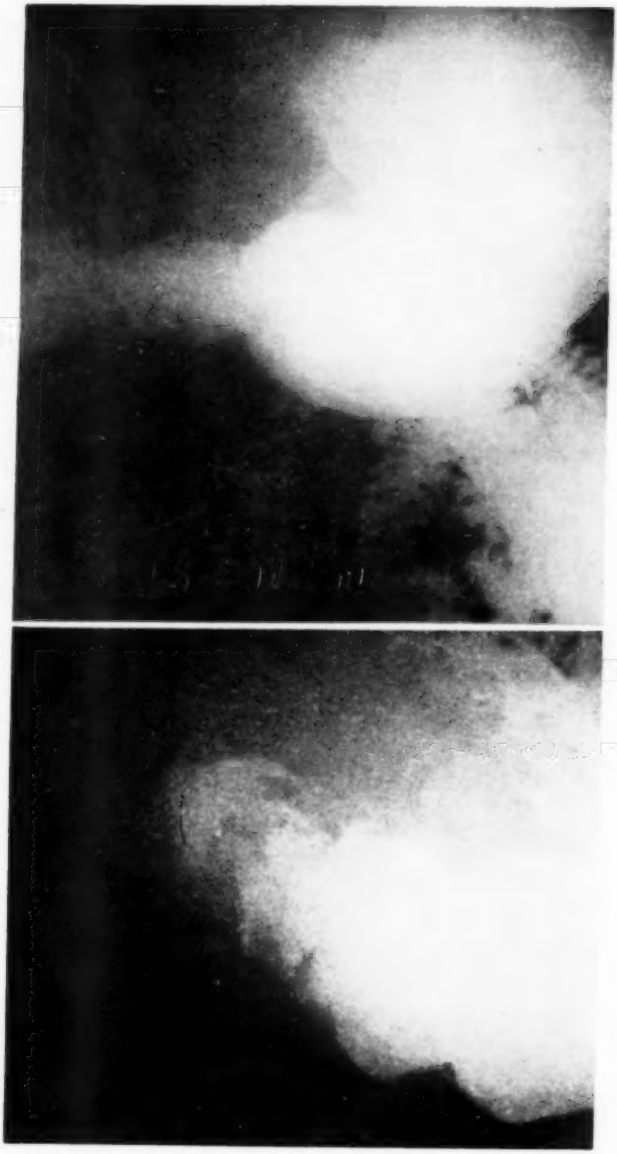


FIG. 5. Serial views of opacified stomach and proximal duodenum (January 18, 1946) denoting polypoid mucosal changes in the distal antrum and prepylorus with herniation of these mobile rugae into the base of the duodenum. No ulcer crater was identified.

diet. The patient reported that in March 1945 he had experienced pain in the chest and had dyspnea. He was taken to Emergency Hospital, Milwaukee, per ambulance where he received a number of "shots." He was dismissed the following day and returned to work. He continued to work until June 1945 when he was referred to St. Joseph's Hospital, Milwaukee for electrocardiographic study. The report stated "chronic coronary disease and serious myocardial impairment." He was subsequently advised to do only light work.

Roentgen studies were first performed on January 18, 1946 and again on February 8, 1946. Preliminary fluoroscopy of the chest in January revealed slight to moderate enlargement of the left ventricle. The barium filled esophagus was neither displaced nor encroached upon. The prepyloric and distal antral mucosal pattern was exaggerated, polypoid-like changes being present. Considerable mobility of the prepyloric mucosal folds was discovered and prolapse into the base of the duodenum (figure 5, a and b) was demonstrated during serial studies. No ulcer crater was seen and gastric motility was not delayed. A small diverticulum was seen in the second portion of the duodenum.

Oral cholecystography failed to opacify the gall-bladder. No radiopaque calculi were seen. The interpretation of lack of gall-bladder visualization in view of the cardiac status and prolapse was difficult. Barium enema studies revealed no pathologic lesions in the colon or terminal ileum.

The patient returned February 8, 1946 for repeat barium studies. No prolapse of the mucosa was seen at this time but the mucosal findings were essentially unchanged. The patient failed to return to the referring physician after the second series of roentgen studies but we have been informed that he died at home early in the year 1947.

Comment. In this patient with severe myocardial damage and mild right heart failure one can attribute the changes in the stomach to decompensation with subsequent prolapse. A bleeding point was not found during roentgen studies of the upper gastrointestinal tract. The site of origin of the hematemesis (cupful of blood) two weeks prior to roentgen-ray examination was not determined; there is at least a slight possibility that an erosion in the prolapsing portion of the mucosa of the stomach gave rise to such bleeding.

Discussion

That cardiac disease can be responsible for gastric complaints is not doubted. Since congestive heart failure occurs more frequently in the aged, prolapse of the gastric mucosa on such a basis could not be expected to occur with any great frequency in younger groups. Scott [21] does not mention the age of the patient who evidently died in heart failure and exhibited folds of gastric mucosa almost as edematous and mobile as those in one of our cases (case 2, figure 2, a and b). No roentgen studies were made in Scott's case. In an as yet unreported group of 50 successive cases of prolapsed gastric mucosa (A. M., [14]), the youngest patient was 17 years of age and the oldest 69. Scott reported that prolapse of the mucosa was found in 1.04 per cent of the total number of gastrointestinal examinations performed, equalling the incidence of gastric ulcer in his group. In our experience this condition seems to be more frequent than benign gastric ulcer. On the other hand, herniated gastric mucosa occurred in several patients with peptic ulcers, as mentioned by Scott.

Ten per cent of 1,500 cardiac patients in Flaxman's [8] series had symptoms referable to the gastrointestinal tract. Fifty per cent of these patients had such complaints prior to the cardiac symptoms and in only 1.8 per cent was there associated "gastrointestinal pathology." The basis and criteria for the latter statement are not known; whether all of his patients received the benefit of roentgen investigation is not mentioned. Interestingly enough, one of the major complaints recorded by Flaxman was vomiting not preceded by nausea, and this symptom cleared when relief of the congestive heart failure was effected by digitalis. It would be worthy of trial, at least so far as gastric physiology is concerned, to perform barium meal examination in such patients during phases of decompensation and to ascertain later when compensation was effected if these changes were reversed.

Three main theories have been promulgated for the etiology of prolapsed gastric mucosa: (1) Eliason and Wright [6, 7] believe that prolapse follows hypertrophy of the folds of the stomach after mild inflammatory states. These folds are eventually carried into the duodenum by peristaltic waves. (2) Rees [18] suggests that prolapse of the mucosa follows narrowing of the pyloric ring after which hyperperistalsis and hypertrophy cause the prolapse. (3) Forssell [9] first described an active movement of the gastric mucosa independent of the contraction of the mucularis and Golden [10] enlarged on this concept to advance the third main theory, that of failure of the normal "stretching mechanism" during antral peristalsis resulting in prolapse of the prepyloric rugae.

Factors capable of producing right heart failure might be held responsible, indirectly, for the production of prolapse of the gastric mucosa. The following cor pulmonale syndromes in addition to the other known causes of right heart failure should be capable of predisposing to prolapse: pulmonary fibrosis, chronic emphysema, Ayerza's disease, primary pulmonary vascular sclerosis, silicosis, etc. A similar pathologic state such as the Bernheim syndrome can, at least theoretically, lead to prolapse.

In cases 1 and 2 reported above and studied at post mortem, the basis for the rugal changes and prolapse were different. In the first patient, the prolapse was evidently secondary to a congestive state of the stomach following myocardial infarction and cardiac decompensation. The major complaints of the 56 year old white male were indigestion, epigastric pain and vomiting. Grossly, the stomach wall was thickened and the rugal folds were redundant and increasingly mobile. There were no erosions or ulcerations of the mucosa. The gall-bladder was normal and no biliary calculi were present. The liver exhibited chronic passive congestion. The roentgen findings, consisting of a defect in the base of the duodenal bulb with rugal markings extending from the stomach into the duodenum, were indicative of a small prolapse of the mucosa (figure 1). We believe that it is reasonable to assume that the digestive symptoms were traceable or directly attributable to the herniation of the mucosa.

The second patient, a 75 year old white male, with a long asthmatic his-

tory was not examined roentgenographically but the postmortem findings were so outstanding that no one could reasonably doubt that prolapse of the gastric mucosa had occurred during life. This patient had been a chronic asthmatic and entered the hospital with signs and symptoms of progressive right and left heart failure and died 36 hours after admission. Here, a cor pulmonale syndrome led to the right heart failure. The large, almost giant-sized gastric rugae could easily be swayed proximally or distally, in the latter case actually "flopping" across the pylorus (figure 2, a and b). The pyloric ring is clearly demarcated by arrows. On one hand, the folds lie proximally while, on the other hand, the markedly redundant folds are seen to extend beyond the pyloric ring into the duodenum. Microscopic sections (figure 3, b and c) reveal congestion and edema of the mucosa and submucosa and the presence of eosinophiles and plasma cells. The gross and microscopic findings are compatible with a diagnosis of "congestive gastritis."

The second group of patients, cases 3 and 4, confirmed neither at autopsy nor on surgery, presented clinical signs of right heart failure with cardiac enlargement. The first patient of this group (case 3) is an example of decompensated heart disease early in our period of observation. The roentgen appearance of the stomach and duodenum was due to prolapse of the gastric lining. Case 4 provides another example of arteriosclerotic heart disease, decompensation and prolapse of the gastric mucosa. This patient died soon after the roentgen studies. In all our cases, the "gastric" symptoms seem to be due, at least in part, to prolapse of the redundant folds.

Gastrointestinal symptoms in heart failure (especially of the right heart failure type) can be caused by involvement of different organs. Varying disturbances in physiology may thus result. However, there has been no mention in the literature regarding prolapse of the gastric mucosa as a possible cause of these symptoms in some cases. Gastric function is altered inasmuch as there is decreased motor, secretory and absorptive function in right heart failure with congestion. The total and free acid are lower than normal and there may be anacidity. In congestive heart failure, there is much mucus in the gastric secretions in addition to the low acid secretions (Bologna and Castadoni,[4] Niehaus,[16] Rehfuss[19]). Nevertheless, anacidity in the majority of instances gives rise to no symptoms and is compatible with perfect health (Best and Taylor,[2] A. J. Carlson[5]) except, of course, when associated with such pathologic states as pernicious anemia, carcinoma of the stomach, chronic gastritis and possibly prolapse of the gastric mucosa. Carlson states that the rôle of the gastric juice in the maintenance of health has been exaggerated to the neglect of normal motility. We may therefore conclude that the changes in the secretion are of minimal importance in producing symptoms in right heart failure. Whether involvement of the liver by the congestive process is enough to produce symptoms other than right upper quadrant pain is difficult to say. Probably, when the insults are severe or oft repeated, a "congestive cirrhosis" appears and symptoms can be caused by the central fibrosing process and the hepatocellular damage. Liver

function returns to normal, however, in most instances where the congestive heart failure is relieved. The external and internal secretions of the pancreas also seem to be diminished in peripheral congestive failure but little is to be found in the literature concerning this phase (Bologna and Castadoni [4]). Scott [21] describes one case of severe cardiovascular disease in which he found at postmortem examination very redundant gastric rugae, and he proposes that prolapse of these folds was the probable cause of the patient's gastric symptoms. Scott, however, makes no mention as to whether the patient died in congestive heart failure. In his case as in our case 1, the gall-bladder was of normal appearance at autopsy.

The roentgen aspects of prolapsed gastric mucosa have been adequately dealt with in various publications, comprehensively and recently by Scott. [21] The typical appearance of the prolapse in the duodenal bulb is that of a central "mushroom" or "cauliflower-like" negative shadow, or, as we like to designate it now, an "atomic bomb" appearance in those cases in which a cuff-like prolapse occurs. One also observes a peculiar deformity of the distal stomach due to "tugging" by the slipping or movable gastric folds. It is worthy of emphasis to state that if cases of prolapsed gastric mucosa are not to be overlooked, it is essential to perform serial studies as a part of all investigations of the upper gastrointestinal tract. In our experience there were many instances in which only one or two of 8, 12 or 16 serial views revealed a prolapse while the other projections did not. We have come to the conclusion that the right lateral recumbent position for such studies offers optimum conditions for the study of the distal stomach and duodenal bulb and for the demonstration of prolapses of the gastric mucosa.

Summary

Four cases of right heart failure in which redundancy of the prepyloric rugae of the stomach was found are reported. In all of these patients gastrointestinal symptoms were present. It is believed that the pathologic changes in "congestive gastritis," at least in some cases of right heart failure, predispose to prolapse of the gastric mucosa. That prolapse of the gastric mucosa can cause symptoms cannot be denied. There seems to be a definite correlation between right heart failure and "gastric" symptoms in such right heart failure. Since cardiac decompensation is reversible in many cases, so might prolapsed gastric mucosa be where the basis for its presence can be attributed to congestion of the peripheral circulation.

We are indebted to Dr. J. Arendt of the Department of Radiology, Mount Sinai Hospital, Chicago for his kind cooperation and permission in making the roentgenograms of case 1 available for publication.

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AEROSOL PENICILLIN IN ALLERGIC PATIENTS WITH RESPIRATORY INFECTIONS*

By MAYER A. GREEN, M.D., F.A.C.P., *Pittsburgh, Pennsylvania*

THE inhalational administration of antibiotics and chemicals has developed into a practicable and effective approach in the treatment of certain respiratory tract diseases.

The advent of penicillin with its unique capacity for nebulization lent impetus to the application of this technic and to the accumulation of scientific data pertaining to the bacteriology and physiology of the respiratory system. The distribution and remarkable absorptive capacity of the respiratory tract mucous membrane provide a wide area for the topical application and absorption of aerosolized penicillin.

The clinical application of aerosolized penicillin has been based on certain fundamental and essential observations such as those of Bryson, Sonsome, and Laskin.[1] These investigators affirmed that the chemical and bacteriostatic properties of penicillin are not altered when it is transformed into an aerosol. Further work by Segal [2] suggested that the topical effectiveness of aerosol penicillin is not dependent on the penicillin blood level. On the other hand, it has been amply demonstrated by Humphrey and Joules [3] that satisfactory penicillin blood levels can be reached with aerosol administration. Barach, Garthwaite, and Rule [4] emphasized penicillin's effective bacteriostatic power against streptococcus and staphylococcus, and that this action was not inhibited by purulent secretions or para-aminobenzoic acid.

Logical developments were the combination of penicillin with other drugs such as vasoconstrictors, bronchodilators, and bactericidals. Abramson [5] combined penicillin with hydrogen peroxide in the treatment of lung infections.

An editorial comment in the Journal of the American Medical Association [6] sounded a justifiable note of caution in regard to the empirical evaluation of the effectiveness of this procedure, and requested the amassing of further data in larger groups of properly studied and adequately controlled cases.

In line with these thoughts, this report is offered. It covers a one-year period of observation from October, 1946 to October, 1947 with the use of aerosol penicillin as an adjuvant therapeutic measure in the management of allergic patients with acute and chronic diseases of the upper and lower respiratory tracts. Over 200 aerosol treatments were administered to 79 allergic patients with various respiratory allergies.†

* Received for publication February 24, 1948.

† Since this report was originally compiled, approximately 300 aerosol penicillin treatments have been administered to 128 allergic patients. The previous findings have been confirmed.

The aerosol penicillin treatment, described herein, was undertaken solely as an office and home procedure in ambulant patients. When indicated, it was supplemented by the self-administration of aerosol penicillin at home, by oral penicillin, or by intramuscular injections of large doses of penicillin in oil and wax. Since the procedure was undertaken as a home and office method, no bacteriologic studies or penicillin blood level determinations were undertaken.

Apparatus and Material Employed

A number 200 Pen-i-sol nebulizer (Oxygen Therapy Company, Los Angeles, California), pictured below, was utilized. It consists of a glass nebulizer, rebreathing bag, and closely fitting oronasal face mask. The

Fig. 1. The No. 200 Pen-i-sol Inhaler, with breathing bag and mask.

nebulizer is reported to convert penicillin solutions into particles finer than one micron in diameter. The glass nebulizer has a unique retort shape which allows the anterior wall of the nebulizing chamber to serve as the splash wall, preventing the droplets from being included in the stream of nebulin produced, and forcing any droplets back to the cone-shaped liquid area for nebulization. The closely-adapting mask minimizes waste and allows treatment through the nose or mouth or both. The breathing bag acts as a reservoir for comfortable breathing and retention of exhaled nebulin. No valve cut-off or "Y" is necessary. It has proved readily applicable to the very young or sick patient, since he may assume a passive rôle during the procedure.

The nebulizer is connected by rubber tubing to an oxygen tank. The penicillin is driven through the circuit under positive oxygen pressure at a

rate readily controlled by the valve gauge attached to the oxygen tank. The large floor model oxygen tank was found to be most convenient.

The sodium salt of penicillin was used. In all the aerosol treatments there was not a single instance of local irritation of the mucous membrane of the nose and throat which could be attributed to the penicillin preparation used. Five cubic centimeters of sterile aerosol stock solution were added

FIG. 2.

to vials containing 100,000 units of penicillin, thus providing 20,000 units per cubic centimeter. The aerosol stock solution was prepared by adding 99 cubic centimeters of distilled water to 1 cubic centimeter of 10 per cent laboratory aerosol solution. Laboratory aerosol 10 per cent (made by Fischer Scientific Company) is a water-clear, mobile liquid containing Aerosol O. T. (di-octyl-sodium sulfosuccinate, a mutual solvent, and water). Aerosol has a complex chemical structure and is made up of two essential parts—the "hydrophilic," that portion which is attracted to water, and the "hydrophobic," that portion which is attracted to an oil or other non-polar medium. Thus, Laboratory Aerosol 10 per cent enables water to come into contact with other substances more quickly, and wets them more thoroughly. Aerosol is neutral in chemical reaction and is stable at room temperatures.

Aerosol penicillin was prepared in 5 cubic centimeter quantities, when necessary, stored in the refrigerator, and used within two or three days.

TECHNIC FOR, AND OBSERVATIONS DURING, THE ADMINISTRATION OF AEROSOL PENICILLIN

The patient was seated on an examining table in a comfortable position, the head supported by the elevated portion of the table, the feet resting on

the foot ledge. The head rest was adjusted individually to permit a posture most suitable for proper respiration. Nasal tamponage was applied where shrinkage of the nasal mucous membrane was necessary to promote drainage and ventilation, and to permit the penicillin to reach the deeper infected tissues. However, it was repeatedly observed that a salutary shrinkage was achieved by the inhalation of oxygen alone, or in combination with aerosol penicillin. The use of the vasoconstricting nasal tampons, on the other hand, provided a more effective and lasting shrinkage.

The face mask was comfortably and securely fastened. Ten to twenty thousand units of aerosol penicillin were injected into the nebulizer. When a local antihistaminic effect was desired, as in cases of acute pollinosis, 0.2 cubic centimeter of 2 per cent pyribenzamine hydrochloride was added. When the patient required the antiasthmatic effect of epinephrine, it was added, usually as 0.2 cubic centimeter of 1:1000 solution of epinephrine hydrochloride. The 1:100 solution of epinephrine hydrochloride utilized by the aerosol technic caused a marked blanching and irritant effect on the nasal mucous membrane; its use, therefore, was abandoned. A group of patients, not included in this report, is being studied, using 0.25 per cent neosynephrine hydrochloride as the vasoconstricting agent.

The oxygen pressure gauge was set at 4.5 liters per minute. The patient was instructed to take deep inspirations every second or third breath, holding the inspiration as long as possible, followed by a deep and full expiration. He was cautioned not to force the respirations at a too rapid rate, in order to prevent the effects of hyperventilation. The average patient required five minutes to utilize completely 10,000 units of aerosol penicillin and 0.2 cubic centimeter of epinephrine or pyribenzamine. The time varied between five and eight minutes, depending on the age and size of the patient, the respiratory rate, amplitude of respirations, and the presence or absence of bronchial asthma. The patients were advised not to suppress coughing. Following this treatment, many asthmatic patients noted increased productive coughing, after which the respirations became wheeze-free. Occasionally, a few of those with shallow respirations developed coarse wheezing râles. This was felt to be due to bronchodilation with freeing of secretions into the alveoli and bronchial lumina. The wheezing usually disappeared promptly following expectorant coughing.

As a general rule, in patients with upper respiratory infections complicating a basic respiratory allergy, as hay-fever or allergic rhinitis, three daily treatments were adequate. As previously mentioned, supplemental penicillin was prescribed for home use orally or by inhalation. One hundred thousand units of penicillin were prescribed in 5 cubic centimeters of aerosol solution, to be administered with a De Vilbiss No. 40 nebulizer, 20 inhalations every half-hour. When the infection was of longer duration and greater intensity with definite evidence of acute sinusitis or bronchitis, 300,000 units of penicillin in oil and wax were injected intragluteally daily as

necessary. Nose and throat consultations were sought in all cases of acute and chronic sinusitis for more definitive sinus drainage.

It should be mentioned that these patients all received concomitant anti-allergic management, including specific therapy and allied drug therapy. No reaction attributable to the aerosol penicillin was noted following specific pollen, dust, or vaccine therapy, as previously reported by Vermilye.[7]

Several patients who were seen within 24 hours following the onset of an acute upper respiratory infection observed a dramatic symptomatic improvement, accompanied by a marked abbreviation of the usual course of this infection. This suggests a prophylactic rôle of aerosol penicillin in aborting and limiting the effect of upper respiratory infections. This feature must, of course, be subjected to further critical analysis.

All the patients were studied thoroughly from the combined medical and allergic viewpoint. This included the taking of complete medical histories and the performance of complete physical examinations with fluoroscopic studies of the chest and transillumination of the sinuses. The following procedures were routinely done: urinalyses, complete blood counts, blood sedimentation rates and vital capacity studies before and after penicillin therapy, serological tests, and allergen skin testing. Nose and throat consultations, bronchoscopic examinations, bronchograms, and roentgenograms of the chest were obtained in selected cases.

Careful choice was made of patients to receive the aerosol penicillin therapy. The treatment was restricted to those with respiratory allergies complicated with acute or chronic secondary infection of the respiratory tract, where the bacteriostatic effect of topically and systemically applied penicillin was considered to be of some aid in the control of the infection.

In all, aerosol penicillin treatments were given to 79 patients with various respiratory allergies complicated by secondary infection of the respiratory tract.

Table 1 illustrates the age and sex distribution of the treated cases.

TABLE I

Age and Sex Distribution

Sex	Age in Decades							
	1st	2nd	3rd	4th	5th	6th	7th	Total
Male	5	6	7	2	6	5	3	34
Female	1	4	11	20	5	4	0	45

Those treated with aerosol penicillin are divided into the following diagnostic classifications:

1. Bronchial asthma with respiratory infection (nasopharyngeal and bronchopulmonary)—42 cases.

2. Acute pollenosis (hay-fever) with acute rhinitis and rhino-sinusitis—8 cases.

3. Allergic rhinitis with superimposed rhino-sinusitis—29 cases.

The criteria of response to aerosol penicillin were as follows:

1. Gross alteration in the appearance of the nasal mucous membrane.
2. Increase in vital capacity.
3. Reduction in blood sedimentation rates.
4. Apparent immediate clinical improvement, objectively and subjectively.
5. Comparison with the usual clinical course of previous respiratory infections not treated with aerosol penicillin.

A schematic record of the patients treated in this manner is shown in table 2.

It will be noted in table 1 that the distribution between the sexes is fairly equal in all decades except for the fourth where almost 50 per cent of the female patients is found. No particular significance is attached to this observation.

Twenty-five patients were treated with aerosol penicillin alone; 37 received combined aerosol penicillin and epinephrine hydrochloride; and 19 received aerosol penicillin and pyribenzamine hydrochloride.

It is of interest to record that, in this series, unpleasant side effects were noted in only two cases. In both, the reactions were attributed to epinephrine effect and consisted of palpitation of the heart. The first occurred in case 3, an extremely apprehensive male patient with chronic bronchial asthma. The second occurred in case 75, a young woman with bronchial asthma secondary to an acute upper respiratory infection, who was known to be extremely sensitive to epinephrine. The reactions were of brief duration, subsiding spontaneously.

None of the cases showed blackening of the teeth, gums, or tongue, or irritation of the upper respiratory tract, as has been reported by other observers. There were no immediate or delayed allergic reactions attributable to the aerosol penicillin. In fact, it is felt that the concomitant administration of epinephrine and pyribenzamine serves to reduce the possibilities for immediate constitutional reactions and to enhance the topical effect of penicillin.

To the best of my knowledge this is the first report where laboratory aerosol solution is the diluent used in the preparation of the penicillin.

It must also be noted that observations of the blood sedimentation rates are not a reliable index of the clinical efficacy of the procedure employed. No change in this rate should be anticipated unless one is certain that it is due entirely to infection within the respiratory tract which can be reached by adequate and effective concentrations of penicillin, and caused by penicillin-sensitive organisms. Where a remote focus of infection is responsible for

TABLE II

No.	In.	Sex	Age	Diag.	No. of Treat.	Sed. Rate	V.C. Bef.	V.C. Aft.	P.B.Z.	Ep. HCl 1:1000	Remarks
1	I. L.	F	33	B.A. A.R. H.F.	6		2.8 l.			x	Improved; irritation of nasal m.m. with Ep. HCl. 1:100.
2	A. L.	F	55	B.A. A.R. H.F.	10	10 mm.	2.1	3.1 l.		x	Improved; aer. pen. at home.
3	M. G.	M	61	B.A. H.F. Pulm.Fib. Bronch.	1	5				x	Epinephrine reaction; palpitation and precordial pain.
4	R. S.	F	33	B.A.	4	8	1.8	2.8		x	Improved temporarily; aer. pen. at home.
5	J. B.	M	60	B.A. H.F.	4	20 20	2.3	3.1		x	Improved; aer. pen. at home.
6	M. Z.	M	13	A.R. B.A. H.F.	2						Remarkable improvement.
7	S. R.	M	52	B.A. S.	4	14 11	2.3	3.5		x	Improved.
8	M. L.	M	26	A.R. S.	4	6					Improved.
9	T. S.	F	32	A.R. U.R.I.	5	10 5			x		U.R.I. controlled; nasal pen.
10	M. G.	M	62	B.A. Pulm.Fib.	3	8	2.6	3.0		x	Little relief.
11	J. R.	F	40	A.R. H.F. U.R.I.	1						Control of U.R.I.
12	G. H.	M	43	A.R. U.R.I.	1						U.R.I. controlled.
13	M. C.	F	31	B.A. A.R. H.F. S.	5	4	2.4	3.4		x	Improved.
14	M. G.	M	43	B.A. H.F. U.R.I. Neph.	8	27 27	2.3	3.4		x	Improved.
15	J. K.	M	47	B.A. A.R. H.F. S.	7	18	2.6	4.1		x	Temporary relief.
16	B. H.	F	22	B.A. U.R.I. H.F. S.	1	10	2.4			x	U.R.I. controlled; improved considerably.
17	R. G.	F	32	B.A. S.	3	23	2.3	3.2		x	Improved slightly.
18	M. S.	M	44	B.A. U.R.I. H.F.	2	7	3.2	3.4		x	Much improved.
19	R. L.	F	33	B.A. A.R. H.F.	2	14					Improved; aer. pen. at home.
20	P. M.	F	25	A.R. U.R.I.	3	10					U.R.I. controlled.
21	A. T.	F	40	B.A. U.R.I.	1	23		3.2		x	Control of U.R.I.

TABLE II—*Continued*

No.	In.	Sex	Age	Diag.	No. of Treat.	Sed. Rate	V.C. Bef.	V.C. Aft.	P.B.Z.	Ep. HCl 1:1000	Remarks
22	B. M.	M	46	B.A. A.R. H.F. S.	1	5	4.0	4.3			Improved; nasal pen.
23	G. R.	F	38	A.R. S. U.R.I.	3						Improved.
24	K. K.	M	8	B.A. U.R.I. S.	1						Improved; oral pen.
25	G. S.	F	40	B.A. A.R. S.	1	19		2.1			Temporary relief.
26	S. M.	F	21	B.A. U.R.I.	1		2.4	2.8		x	Improved; aer. pen. at home.
27	L. W.	M	14	B.A. S.	3						Improved; nasal pen.
28	J. K.	M	52	B.A. S.	4	15 15	2.5	2.6		x	Improved.
29	S. L.	M	6	B.A. U.R.I.	1						Improved.
30	M. D.	M	51	B.A. U.R.I.	2						Improved.
31	A. B.	F	29	B.A. A.R.	3	5	1.0	3.4			Improved.
32	R. E.	F	30	A.R. S.	1	18					Improved.
33	H. M.	F	46	B.A. A.R. H.F.	3	7	2.9	3.0	x		Improved.
34	C. C.	M	56	B.A.	1	6	3.0	3.1			Improved.
35	B. R.	F	33	A.R. H. F. S.	2	10 6			x		Improved.
36	L. E.	M	25	B.A. A.R.	4	10	4.0	4.2		x	Improved.
37	D. U.	M	7	H.F. U.R.I.	1						Improved.
38	D. W.	F	26	B.A. A.R. H.F.	4	18	1.8	2.5		x	Improved.
39	E. R.	F	16	B.A. H.F. U.R.I.	1						Improved.
40	B. S.	M	17	H.F. U.R.I.	1						Improved.
41	A. S.	F	31	A.R. S.	1	22 11	3.0	3.5			Improved; nasal and oral pen. at home.
42	M. S.	F	21	B.A. A.R. H.F.	16	25 18	2.8	3.0		x	Improved; aer. pen. at home.
43	I. B.	M	36	A.R. S. U.R.I.	3	7				x	Improved.
44	W. S.	F	49	B.A. A.R. S.	3	11	1.8	2.9		x	Improved; aer. pen. at home.

TABLE II—*Continued*

No.	In.	Sex	Age	Diag.	No. of Treat.	Sed. Rate	V.C. Bef.	V.C. Aft.	P.B.Z.	Ep. HCl 1:1000	Remarks
45	A. Z.	F	34	U.R.I. A.R. B.A.	1	11				x	Improved; nasal and oral pen.
46	M. F.	F	37	B.A. A.R. S.	5	20			x	x	Improved.
47	M. G.	F	29	B.A. A.R. U.R.I.	2	10	2.5	3.6		x	Improved.
48	M. F.	F	56	B.A. U.R.I. Br.	1					x	Temporary relief.
49	U. D.	F	50	B.A. U. R. I. A.R.	8	18	2.0	2.9		x	Improved.
50	S. D.	M	26	H.F. U.R.I.	1	3.5	?.1	4.1			Improved.
51	S. K.	F	30	B.A. U.R.I.	3					x	Improved.
52	D. W.	F	32	A.R. U.R.I.	1	5			x		Improved.
53	A. H.	M	38	H.F. B.A. U.R.I.	2					x	Improved.
54	M. K.	M	17	B.A. U.R.I.	4	6	2.8	4.0		x	Improved.
55	E. H.	M	54	B.A. A.R. S.	7	6	2.4	3.2		x	Improved.
56	M. W.	F	57	A.R. U.R.I.	2	20			x		Improved.
57	S. A.	M	22	B.A. H.F. U.R.I.	4	4	4.8	5.0		x	Improved.
58	N. M.	M	10	B.A. H.F. U.R.I.	1	20 15	1.6	2.2		x	Improved.
59	J. W.	F	36	H.F. U.R.I.	1				x		Improved.
60	R. P.	F	21	B.A. A.R. U.R.I.	2	13			x		Improved.
61	M. S.	F	20	A.R. U.R.I.	1	12			x		Improved.
62	A. S.	F	17	A.R. U.R.I.	3	11			x		Temp. improvement.
63	L. S.	M	42	B.A. A.R. H.F.	4		3.4			x	Immediate relief only.
64	B. K.	F	27	St.A. S.	2	21 13	1.6	2.8	x		Improved.
65	M. H.	M	22	A.R. U.R.I.	2	6			x		Improved.
66	D. H.	F	18	A.R. U.R.I.	3				x		Improved.
67	I. S.	F	30	B.A. A.R. H.F.	2	12	2.8	3.0		x	Improved.

TABLE II—*Continued*

No.	In.	Sex	Age	Diag.	No. of Treat.	Sed. Rate	V.C. Bef.	V.C. Aft.	P.B.Z.	Ep. HCl 1:1000	Remarks
68	H. L.	M	22	H.F. U.R.I.	2				x		Improved.
69	R. C.	F	33	B.A. H.F. U.R.I.	6	22	3.2	3.3	x	x	Improved.
70	C. V.	F	25	A.R. U.R.I.	1	8			x		Marked relief.
71	J. M.	F	39	U.R.I. A.R.	4	16			x		Improved.
72	S. B.	F	5	U.R.I. B.A.	2						Unimproved (uncooperative).
73	E. G.	M	23	B.A. U.R.I.	1						Improved.
74	N. B.	M	4	A.R. U.R.I.	1						Slight improvement.
75	S. L.	F	14	B.A. U.R.I.	4	8				x	Marked improvement.
76	V. K.	F	42	A.R. H.F.	1				x		Improved.
77	L. H.	M	5	A.R. U.R.I.	2				x		Improved.
78	S. F.	F	37	B.A. U.R.I.	1						Improved; aer. pen. and pen. I.M.
79	M. H.	M	15	B.A. U.R.I.	1		2.2	2.2		x	Improved.

KEY TO TABLE II

In.—Initials
B.A.—Bronchial asthma
A.R.—Allergic rhinitis
U.R.I.—Upper respiratory infection
Bronch.—Bronchiectasis
H.F.—Hay fever
S.—Sinusitis
Pulm.Fib.—Pulmonary fibrosis
Neph.—Nephritis
V.C.—Vital capacity
Bef.—Before aerosol penicillin
Aft.—After aerosol penicillin
P.B.Z.—Pyribenzamine hydrochloride
St.A.—Status asthmaticus
Br.—Bronchitis
Ep. HCl—Epinephrine hydrochloride
l.—liters
I.M.—Intramuscular
Aer. Pen.—Aerosol penicillin
Sed. Rate—Sedimentation rate
Diag.—Diagnoses

the sedimentation rate, this site may be unaffected by the penicillin, and the rate remains the same. Case 14 is that of a male patient with chronic glomerulonephritis whose sedimentation rate remained essentially unchanged even after large doses of penicillin intramuscularly in addition to aerosol penicillin; however, there was a slight reduction in the rate of fall during the first few minutes. The factors which influence the sedimentation rate are numerous and variable. Therefore, it is felt that its value is limited in appraising the benefits from the administration of aerosol penicillin to the series of patients under study. When the rapid sedimentation rate was due solely to the respiratory infection, the control and disappearance of the infection were frequently accompanied by a restoration of the sedimentation rate to normal.

In patients with reduced pulmonary vital capacity due to bronchial asthma or infectious processes in the lungs, the administration of oxygen alone is effective in increasing this capacity. Undoubtedly, this effect was enhanced by the use of bronchodilating drugs. The use of oxygen is felt to be superior to compressed air for the reason mentioned and because of its local effect on the tissues and the improvement in general well-being which follows the increased oxygenation of the blood.

Conclusions

The inhalational administration of aerosolized penicillin by the technic described has proved a useful adjunct in the management of patients with respiratory allergies complicated with respiratory tract infections. The following features pertaining to its use must be emphasized:

1. Ease of administration.
2. Paucity of unpleasant local, general, or allergic side-effects.
3. Immediate improvement noted with improved nasal ventilation and drainage, increased amplitude of pulmonary respiration and vital capacity.
4. Enhances results of specific pollen therapy in hay-fever patients with upper respiratory infections.
5. Provides a method of introduction of other drugs.
6. Applicability to patients in all age groups.
7. Possible rôle in limiting course of upper respiratory infections.

Summary

This survey has been presented with the intention of adding further clinical data to the subject of inhalational therapy. Observations made over a period of one year are reviewed. Over 200 aerosol penicillin treatments were given to 79 allergic patients with respiratory infections.

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NITROGEN BALANCE STUDIES IN CHRONIC PEPTIC ULCER DISEASE*

By THOMAS S. SAPPINGTON, M.D.,† and HENRY L. BOCKUS, M.D., F.A.C.P., *Philadelphia, Pennsylvania*

IN recent years considerable interest has been shown in the nutritional aspects of peptic ulcer therapy. Some authors have not only reminded their readers that the ulcer patient has the same diverse food requirements as other persons, but have claimed special therapeutic value for "hyperalimentation" programs in the treatment of patients with uncomplicated peptic ulcer. Co Tui has emphasized the beneficial effect of a diet containing very large amounts of partially hydrolyzed protein.[1]

There are ample data to demonstrate the importance of a high protein intake in the treatment of a host of chronic illnesses and, in the convalescent period, a number of acute disorders. On the basis of a priori reasoning, therefore, it would appear likely that there would be a similar increase in the protein requirement in patients with *chronic* peptic ulcer. This should be true particularly in those with anorexia, voluntary or prescribed dietary restriction, vomiting or hemorrhage. There is available a rather simple procedure, the study of nitrogen balance, by which the protein requirement of such patients may be easily studied. A review of the literature reveals that there have been few such studies carried out on patients with peptic ulcer. Rather has emphasis been placed on the prompt relief of ulcer symptoms following the institution of the "hyperalimentation" or "high protein feeding" regimen. Symptomatic relief, however desirable clinically, does not prove the previous existence of a protein deficiency or the present existence of an increased protein requirement. The results obtained in this clinic in the management of uncomplicated peptic ulcer utilizing the hourly feeding milk regimen have been equally as good if not superior to the results reported following the use of the "hyperalimentation" regimen. We were of the opinion that if "hyperalimentation" is indicated in the therapy of uncomplicated ulcer its rationale should be substantiated by the demonstration of a nitrogen deficit in these patients. Consequently it seemed desirable to determine whether the average patient with uncomplicated ulcer admitted to the hospital was in nitrogen balance. Patients selected for nitrogen balance study had been hospitalized because of clinical evidence of activity of chronic peptic ulcer disease. Unfortunately patients with very early acute ulcers are seldom hospitalized in these days of crowded hospitals and hence could not be studied.

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† American College of Physicians Research Fellow in Internal Medicine.

Method

Patients suffering from chronic peptic ulcer, who had not recently experienced hemorrhage or severe vomiting were selected for this study. No patient who had been subjected to operation within the preceding three months was included. Otherwise the patients were chosen at random. Their dietary regimen was that ordinarily used on the Gastrointestinal Service of the Graduate Hospital. All food offered was weighed daily as were the refusals. By deducting the refused food from that offered the patient the actual intake was computed and its composition was then calculated from the standard dietetic tables. The protein weight in grams was divided by the factor 6.25 to obtain the corresponding value for nitrogen. The daily fluid intake and output were measured, and appropriate blood chemical determinations were made at frequent intervals. The nitrogen content of each day's urine was analyzed by the macro Kjeldahl technic. Stool specimens were pooled for several days, the total nitrogen content determined by the same technic and this value divided by the number of days to give the average daily nitrogen in the stool. Concentrated hydrochloric acid was placed in all specimen containers to assure an acid medium and thus avoid the loss of nitrogen as ammonia. None of the patients vomited during the balance study and none raised significant quantities of sputum.

Results

The clinical status of each of the five patients studied is indicated in a brief protocol. The results of the metabolic survey of each patient are presented in tabular form and a short comment on the findings in the individual case is made.

Case 1. (Studied through the kindness of Dr. Henry Tumen.) A female, 37 year of age. For the eight years preceding her admission she had had intermittent attacks of epigastric pain radiating to the back and the right side of the abdomen. During the past five years the frequency of these attacks had become very much less and for periods as long as several months she was free of pain. An oral cholecystogram showed numerous non-opaque biliary calculi. There had been jaundice with two pregnancies, one in 1932 and the other in 1935, but at no other time. During the five weeks before admission she had a steady, gnawing epigastric pain made worse by eating but relieved by alkali. For the four weeks prior to admission she had been on a low fat diet. A review of the dietary history indicated that the patient had been consuming about 75 grams of protein and 2100 calories daily during this period.

Physical examination was not remarkable. A review of the laboratory examinations, in addition to those listed in table 1, shows the urine and stool to be normal. The gastric analysis was normal, as were the concentrations of serum amylase and serum lipase. The van den Bergh test and the bromsulfalein dye retention test were normal. The leukocyte and differential counts were normal.

Roentgen-ray examination revealed a normal chest, esophagus and stomach. The duodenum showed moderate deformity of the cap with a constant constriction in the mid-portion. A large constant fleck which had the appearance of an active ulcer was seen in the cap. The small intestines were negative. Biliary calculi had been demonstrated by a previous oral cholecystographic examination.

TABLE I

Case 1, Female, Age 37

Date	Intake					Output				N Balance in Grams	Blood Examinations							Date
	Diet Protein in Grams	Diet Fat in Grams	Diet N in Grams	Calories	Total Fluid in Ml.	Urine Volume in Ml.	Urine N in Grams	Stool Wt. in Grams	Stool N in Grams		RBC Count	Hb. in Grams	Hematocrit	Total Serum Protein in Grams %	Total Serum Albumin in Grams %	Total Serum Globulin in Grams %	Blood Urea N in Ml. %	
2/8											4,100,000	13.5	41	6.80	3.95	2.85	9	2/8
2/9	66.2	32.2	10.5	1282	2140	1225	6.57	202	0.17	+3.8								2/9
2/10	51.5	6.6	8.2	846	2060	930	6.72	Soft	0.17	+1.4								2/10
2/11	68.8	11.6	11.0	1203	2200	lost	lost	brown	0.17	—								2/11
2/12	68.8	11.6	11.0	1203	2020	1625	10.50	formed.	0.17	+0.4								2/12
2/13	80.4	12.1	12.8	1413	1940	1450	8.26	No	0.17	+4.4								2/13
2/14	81.5	16.6	13.0	1324	2020	1095	8.26	blood,	0.17	+4.6								2/14
2/15	74.0	7.6	11.8	1164	1980	1700	7.61	pus or	0.17	+4.1								2/15
2/16	57.5	11.1	9.2	1085	2420	1300	8.74	mucus	0.17	+0.3	4,000,000	13.5	40	6.90	3.98	2.92	11	2/16

TABLE II

Case 2, Male, Age 49

Date	Intake					Output				N Balance	Blood Examinations							Date
	Diet Protein in Grams	Diet Fat in Grams	Diet N in Grams	Calories	Total Fluid in Ml.	Urine Volume in Ml.	Urine N in Grams	Stool Wt. in Grams	Stool N in Grams		RBC Count	Hb. in Grams	Hematocrit	Total Serum Protein in Grams %	Total Serum Albumin in Grams %	Total Serum Globulin in Grams %	Blood Urea N in Ml. %	
5/12											4,430,000	13.0	38	7.52	4.72	2.80	13	5/12
5/13	61.5	50.3	9.8	1054	1500	1200	9.06		2.55	−1.8								5/13
5/14	82.2	67.1	13.1	1408	1950	1250	8.95	1665	2.55	+1.6								5/14
5/15	68.3	55.8	10.9	1169	1675	1270	9.67	Light	2.55	−1.3								5/15
5/16	75.3	61.5	12.0	1290	1790	1455	11.02	brown	2.55	−1.5								5/16
5/17	46.5	38.1	7.4	798	1135	735	8.00	formed.	2.55	−3.1								5/17
5/18								No pus, blood or mucus			4,210,000	13.0	39	7.48	4.81	2.67	14	5/18

The course in the hospital was satisfactory. The patient remained at bed rest. She received hourly feedings when awake of four ounces of the following formula: 100 gm. of calcium caseinate ("casec"), 300 gm. of carbohydrate ("Dexin"), 3 egg whites, 10 ml. of vanilla extract in 1500 ml. of skim milk. She also received 150 mg. of ascorbic acid and 15 ml. of a vitamin B complex concentrate daily by mouth.

Comment: The results of her metabolic study are shown in table 1. There is a consistent low positive nitrogen balance indicating protein storage and previous protein deficiency. This finding is associated with a low urine nitrogen and a moderate nitrogen intake. The stool nitrogen is a low normal.

Case 2. A male, 49 years of age. There had been recurrent episodes of severe, burning epigastric pain with food relief and a typical ulcer pain rhythm for six years following a cholecystectomy. A particularly severe attack of pain led to his admission. He had been on a low fat diet for two months before admission. Review of his dietary history for one month before admission indicated a minimum daily protein intake of 80 gm. and 2500 calories.

Physical examination was not remarkable. Laboratory examination included (in addition to those results recorded in table 2) a normal leukocyte count and differential white cell count. The urine and stool examinations were normal. Gastric analysis showed a fasting hypersecretion, a moderate hyperacidity, and normal gastric emptying.

Roentgen study revealed a normal esophagus, stomach and chest. An ulcer niche was demonstrated in the midportion of the lesser curvature of the duodenal cap. There was also a pseudo-diverticulum.

In the hospital the patient made a satisfactory response to bed rest and four ounces of the following formula given hourly when awake: 80 gm. of skim milk powder dissolved in 2000 ml. of whole milk. No other food was given in the hospital previous to and during this survey. He received 8 ml. of aluminum hydroxide hourly midway between feedings of the formula, and supplementary oral vitamins.

Comment: The results of his metabolic survey are given in table 2. A slight negative nitrogen balance is apparent. It is almost small enough to fall within experimental error. One may conclude, however, that ideally the patient's formula should have been increased to provide at least two more grams of nitrogen daily. We do not know the explanation for the rather elevated fecal nitrogen value.

Case 3. A male, 51 years of age. The patient had been suffering from periodic episodes of mild epigastric pain relieved by milk and soda for two years before admission. His symptoms had been poorly controlled during the two months before admission when he had had frequent night pain, loss of appetite and a weight loss of two pounds. Review of his dietary history during this period indicated that there had been a minimum daily protein intake of 50 gm. and 2600 calories.

Physical examination revealed a well developed and nourished man with minimal tenderness and muscle guarding in the epigastrium. Laboratory examination revealed a normal urine and stool. The white blood cell count, differential count and sedimentation rate were normal. The serum amylase concentration was within normal limits. The gastric analysis showed normal acidity with hypermotility.

Roentgen-ray examination showed a normal esophagus and stomach. In the duodenal cap distortion and deformity of the mucosal pattern were noted. We could not identify a fleck but the configuration of the cap suggested scarring from old ulcer.

In the hospital his symptoms responded readily to bed rest and feedings of four ounces of milk each hour while awake. Ten ml. of aluminum hydroxide gel were given each hour midway between the milk feedings. He also received two vitamin B complex capsules daily. For the period preceding and during the survey he received no other food.

Comment: The metabolic survey is reported in table 3. The patient was in slightly negative nitrogen balance during the test. The low urine nitrogen values are especially noteworthy as they indicate (in the presence of adequate urine volume) the low level of nitrogen excretion seen in patients receiving inadequate protein over a period of time. Under these circumstances the dietary intake should certainly have been greater, both to repair the already existing deficit and to provide a more liberal ration of protein for the maintenance of adequate nutrition after the deficit had been corrected.

Case 4. A male, 39 years of age. This patient had first suffered from duodenal ulcer in 1936, eleven years before entry to this hospital. A posterior gastrojejunostomy had been performed in 1938. Post-operatively he remained well until 1945 when he experienced a return of ulcer symptoms (burning periumbilical pain relieved by vomiting and by the taking of food). Eight months before admission there had been an episode of hematemesis and melena. Two months later he bled again. Four months before admission he was operated upon elsewhere and a lysis of the gastrojejunostomy was done. The patient was told he had had a marginal or jejunal ulcer. Post-operatively he remained well for three weeks, then began to have severe burning epigastric pain radiating to the back which was only slightly relieved by eating. The pain was especially severe at night, interfering with sleep. During the three months before admission to this hospital the diet had been restricted to fluids and light solids. It is estimated that during this period he received an average daily minimum intake of 55 gm. of protein and 2200 calories. He had lost six pounds during this time.

Physical examination revealed a thin individual with no gross evidence of nutritional deficiency. There was moderately severe mid-epigastric tenderness. Laboratory examination revealed normal urine and stools. The white blood cell count and differential cell count were normal. The van den Bergh, serum amylase, serum lipase and bromsulfalein dye retention tests were all normal. The prothrombin time was normal. Further data more pertinent to the metabolic study are reported in table 4.

During the first several weeks of the patient's course it was difficult to control his pain despite the strictest medical regimen. In fact, it was not until six days after the completion of the survey that the patient was consistently symptom-free. He received hourly feedings of four ounces of milk when awake. Ten ml. of aluminum hydroxide gel were given hourly midway between the milk feedings. In addition atropine, phenobarbital and vitamins were administered. He was kept at bed rest. On May 24, because of the persistence of pain, a constant intragastric milk drip was instituted by means of a nasal tube. This was discontinued after one day because of intolerance to the tube. The following formula was used on that one day for the tube feeding: 2040 ml. of skim milk containing 204 gm. of skim milk powder and 204 gm. of carbohydrate ("Dexin"). No other feedings were given on that day. The following day the patient was returned to the hourly milk regimen given by mouth.

Roentgen-ray examination revealed a normal chest and esophagus. In the stomach there was slight distortion of the mucosa in the region of the greater curvature in the mid-portion of the stomach which may have been the site of previous gastrojejunostomy. Slight coarsening of the mucosal pattern of the remaining stomach was

TABLE III

Case 3, Male, Age 51

Date	Intake					Output				N Balance	Blood Examinations							Date
	Diet Protein in Grams	Diet Fat in Grams	Diet N in Grams	Calories	Total Fluid in Ml.	Urine Volume in Ml.	Urine N in Grams	Stool Wt. in Grams	Stool N in Grams		RBC Count	Hb. in Grams	Hematocrit	Total Serum Protein in Grams %	Total Serum Albumin in Grams %	Total Serum Globulin in Grams %	Blood Urea N in Ml. %	
7/14											4,450,000	13.0	40	6.72	3.32	3.40	17	7/14
7/17	39.3	68.4	6.2	1740	2100	1025	6.57	477	0.75	−1.0								7/17
7/18	39.3	68.4	6.2	1740	2100	1355	8.38	Formed,	0.75	−2.9								7/18
7/19								normal stool			4,500,000	13.0	40	6.64	3.45	3.19	17	7/19

TABLE IV

Case 4, Male, Age 39

Date	Intake					Output				N Balance	Blood Examinations							Date
	Diet Protein in Grams	Diet Fat in Grams	Diet N in Grams	Calories	Total Fluid in Ml.	Urine Volume in Ml.	Urine N in Grams	Stool Wt. in Grams	Stool N in Grams		RBC Count	Hb. in Grams	Hematocrit	Total Serum Protein in Grams %	Total Serum Albumin in Grams %	Total Serum Globulin in Grams %	Blood Urea N in Ml. %	
5/20											4,490,000	13.0	41	5.72	3.32	2.40	13	5/20
5/21	73.4	84.0	11.7	1473	2155	1830	13.35	1208	.60	− 2.2								5/21
5/22	127.0	147.0	20.3	2585	3770	1580	8.55	Yellow,	.60	+11.2								5/22
5/23	115.0	131.4	18.4	2306	3375	1575	8.34	formed	.60	+ 9.5								5/23
5/24	144.0	6.0	23.0	2278	2040	570	7.39	milk	.60	+15.0								5/24
5/25	57.1	65.3	9.1	1145	1673	1060	12.62	stool,	.60	− 4.1								5/25
5/26	91.8	106.5	14.7	1842	2692	Lost	Lost	without	.60	—								5/26
5/27	66.8	76.5	10.7	1342	1960	1675	10.22	pus,	.60	− 0.1								5/27
5/28	80.3	91.7	12.8	1610	2352	1932	11.20	blood or	.60	+ 1.0								5/28
5/30								mucus			4,290,000	12.5	38	6.88	4.12	2.76	14	5/30

thought to be due to gastritis. The duodenal cap was moderately deformed with a pseudo-diverticular out-pouching of the greater curvature aspect of the mid-portion of the cap. The remainder of the cap showed moderate distortion of the mucosal pattern believed to be due to cicatrization from previous ulcer. The proximal jejunal loops were dilated and a niche 7.5 cm. distal to the ligament of Treitz was thought to represent a jejunal ulcer. Slight segmentation and flocculation were noted in the small bowel loops which probably represented disturbed motor physiology caused by nutritional deficiency.

Comment: The metabolic survey is presented in table 4. The entire fluid intake for each day represents milk except for one day (May 24) on which the tube formula was the only fluid given. It will be noted that only on two days of the milk feeding (May 22 and May 23) as well as on the day of the tube feeding was the protein intake adequate to effect a significant positive nitrogen balance. This may represent a temporary storage of nitrogen brought about by a sudden increase in the amount of nitrogen given. It will be noted that milk in ordinary amounts (two liters a day) did not supply sufficient protein to this patient to bring about a positive nitrogen balance if a protein deficiency existed. The low serum protein and serum albumin at the beginning of the survey definitely suggest a previous moderate protein deficiency.

Case 5. A male, 46 years of age. The patient had a history of duodenal ulcer disease for 21 years. The first symptom was a perforation which was closed. A gastroenterostomy was done at that time. Since then the patient has had occasional periods of epigastric distress relieved by food. During the two weeks before admission food gave incomplete relief. There had been no evidence of bleeding. His diet for the three years prior to admission had excluded meat (apparently on the advice of a physician), cabbage and fried foods. Review of the dietary history for the two months prior to his admission indicated a daily protein intake of 50 gm. and a caloric intake of 2400.

Physical examination revealed normal urine and stools. The leukocyte count and differential cell counts were normal. Fractional gastric analysis showed a grade 2 hyperacidity with hypersecretion and some motor delay. Insulin gastric analysis showed a maximum free acidity of 126 units and a total acidity of 154 units. Gastroscopy showed an essentially normal stomach. The stoma was not seen. Other laboratory results are listed in table 5.

Roentgen-ray examination on April 23 showed a normal chest and esophagus. The stoma of a posterior gastroenterostomy was seen three inches proximal to the pylorus with moderate distortion of the mucosa around the anastomosis. The duodenal cap was moderately deformed with a pseudo-diverticulum formation. An ulcer niche in the region of the greater curvature of the cap could not be excluded. The cap deformity was characteristic of scarring from ulcer. There was slight coarsening of the mucosal pattern of the proximal jejunum including the region of the anastomosis. A further roentgen examination on May 9 showed these same findings and in addition all of the small bowel loops were slightly dilated and there was moderate motor dysfunction, probably on a nutritional basis.

The patient's course in the hospital was satisfactory with rapid relief of his symptoms on a strict ulcer regimen, including bed rest, antispasmodics and sedatives. His diet consisted of hourly (when awake) five ounce feedings of the following formula with vitamin supplements: 120 gm. of skim milk powder and 120 gm. of carbohydrate added to 1800 ml. of skim milk. In addition he received protein

TABLE V

Case 5, Male, Age 46

Date	Intake						Output				N Balance	Blood Examinations							Date
	Diet Protein in Grams	Diet Fat in Grams	Diet N in Grams	Parenteral N in Grams	Calories	Total Fluid in Ml.	Urine Vol. in Ml.	Urine N in Grams	Stool Wt. in Grams	Stool N in Grams		RBC Count	Hb. in Grams	Hematocrit	Total Serum Protein in Grams %	Total Serum Albumin in Grams %	Total Serum Globulin in Grams %	Blood Urea N in Ml. %	
5/5												4,600,000	13.5	44	6.16	4.05	2.11	14	5/5
5/6	118.8	5.4	19.0	7.2	1924	3870	2505	23.6	714	1.4	+1.2								5/6
5/7	118.8	5.4	19.0	7.2	1924	4072	2265	24.3	formed	1.4	+0.5								5/7
5/8	118.8	5.4	19.0	7.2	1924	4860	2465	25.3	normal	1.4	−0.5								5/8
5/9									milk stool			4,500,000	13.5	43	7.04	4.45	2.59	13	5/9

hydrolysate equivalent to 45 gm. of protein daily intravenously. He was afebrile throughout his stay.

Comment: The results of his metabolic survey are given in table 5. The patient was in normal nitrogen balance during this survey. Despite the dietary history and the question of nutritional deficiency raised by the mucosal pattern of the small bowel there was no storage of nitrogen at this high level of nitrogen intake. This patient was studied 14 days after the high protein diet was begun. It might be argued that a protein deficiency had existed originally and that this deficit had already been corrected by the high protein regimen given over a period of two weeks. We have found, however, that significant protein deficiency requires the prolonged administration of large amounts of protein for its correction.

Discussion

Of the five patients suffering from chronic peptic ulcer disease reported in this paper, Case 1 was found to be in consistent positive nitrogen balance and hence may be considered to have had a previous protein deficiency. Case 4 almost certainly had a significant protein deficiency. That conclusion, however, cannot be proved from the nitrogen balance data in table 4 because of the great daily variation in nitrogen intake and the possibility that the storage of nitrogen recorded on three days may have been temporary. Nevertheless, the low values for total serum protein and serum albumin at the outset of the study definitely suggest previous protein deficiency. Case 3 probably had had a previous protein deficiency but unfortunately insufficient protein was given to allow storage if such were to take place. However, the low urine nitrogen value in this patient suggests the presence of a previous protein deficit. Similarly in Case 2 inadequate protein was given to allow for nitrogen storage if such were to occur. The urine nitrogen value is not high but the patient is actually in slightly negative nitrogen balance because of a low protein intake and a high fecal nitrogen. Because the urine nitrogen in this patient is within normal limits it may be that no previous severe protein deficit existed. Case 5 gave no evidence of previous protein deficit and was in normal nitrogen balance with no nitrogen storage despite the large amount of nitrogen given. In brief, then, two patients had a previous protein deficit, one probably had, one probably did not have and one definitely did not have a previous protein deficiency.

All of our patients had been on suboptimal diets as far as protein was concerned. Anemia was not present in any patient. Total serum protein and serum albumin were definitely low only in Case 4 and borderline in Case 5. In Case 1, showing a definite protein deficit, the deficiency was apparently not sufficiently marked to be associated with an alteration of the serum proteins.

These studies suggest that 15 gm. of nitrogen daily might be a safe minimum intake for patients with uncomplicated peptic ulcer. This is

approximately equivalent to 95 gm. of protein. This value is minimal and of course would have to be modified according to the patient's weight, and increased if there had been previous loss or "toxic destruction" of protein from hemorrhage, shock, vomiting, fever or operation. Review of these data suggest that an intake of 15 gm. of nitrogen probably would have been adequate for the needs of the patients reported in this paper. It should be emphasized that the restriction of the diet to four ounces of milk given hourly while the patient is awake does not meet this minimal requirement. Under ordinary circumstances such a regimen allows the patient approximately two liters of milk daily which provides but 68 gm. of protein or not quite 11 gm. of nitrogen. Hence if the clinician wishes to employ a milk diet for the early treatment of the patient with peptic ulcer it would appear necessary that extra protein be added (e.g., in the form of skim milk powder). In this connection we would like to state that we do not feel that protein hydrolysates, unpalatable and costly as most of them are, offer any advantage over whole protein in the treatment of uncomplicated chronic ulcer.

The rather high incidence of protein deficiency in these patients may in part be due to the fact that they were suffering from chronic peptic ulcer and were admitted to the hospital only after failure of ambulatory treatment. The history of inadequate protein intake immediately preceding admission is doubtless a very important factor in the production of this protein deficiency. Similar studies of ambulatory patients taking unrestricted diets after the appearance of ulcer symptoms would be of great interest.

Summary

The protein requirement of five patients with chronic peptic ulcer has been studied by means of nitrogen balance surveys as well as the more routine chemical analyses. Two of these patients gave evidence of a previous nitrogen deficiency and hence an increased requirement of protein; another patient was probably in a similar state; a fourth patient was probably not suffering from protein deficiency; the fifth patient had no demonstrable protein deficit. Each patient had had a suboptimal protein intake before admission to the hospital. The serum proteins were definitely low in but one patient—one of the two persons shown to have a protein deficiency. Anemia was not present in any patient. It should be emphasized that in all of these cases satisfactory relief of symptoms and ulcer healing took place despite the fact that the diets given some patients were deficient in protein. We are advocating the administration of a moderate surplus of protein to these patients and feel that it is not necessary to prescribe excessive amounts of protein for patients in moderate nitrogen deficit in order to accomplish ulcer healing. Fifteen grams of nitrogen or 95 gm. of protein are suggested as a minimum daily intake for patients in this group. If the diet is to be restricted to milk, a food substance rich in whole protein (e.g., calcium caseinate or skim milk powder) should be added to meet this requirement.

The oral administration of protein hydrolysates would seem to offer no advantage over whole protein in these patients.

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NITROGEN METABOLISM IN CHRONIC IDIOPATHIC ULCERATIVE COLITIS AND ITS THERAPEUTIC SIGNIFICANCE *

By THOMAS S. SAPPINGTON, M.D.,† *Washington, D. C.*, and HENRY L. BOCKUS, M.D., F.A.C.P., *Philadelphia, Pennsylvania*

INTRODUCTION

WE have undertaken a preliminary study of the protein requirement of patients suffering from chronic idiopathic ulcerative colitis. The problem has been approached by means of the familiar nitrogen balance determination together with measurement of the serum proteins, blood urea, red blood cell count and hematocrit. Blood volume studies could not be made. No attempt has been made to consider the question of protein metabolism in detail, but rather we have confined our interest to the over-all exchange of nitrogen.

Recently, the importance of high protein diets in treatment of a host of diseases has been emphasized. The benefit of such dietary regimens in tissue repair has been shown. It would seem reasonable to suppose that many patients having chronic idiopathic ulcerative colitis are deficient in protein. The disease might be expected to cause an increase in the excretion of fecal nitrogen and at the same time a decrease in protein intake due to anorexia, nausea and vomiting. If such a protein deficiency existed commonly in these patients it, alone, might be sufficient cause for the failure of their lesions to heal.

Others have called attention to the therapeutic benefit of high protein administration in patients with chronic ulcerative colitis, especially in the form of protein hydrolysates given orally or parenterally.[1, 2, 3, 4] It seemed desirable to study quantitatively the nitrogen exchange in such patients—to note the incidence of protein deficiency, to measure the fecal nitrogen and the extent to which it is increased by high protein diets, to determine the efficiency with which added protein is utilized in the correction of deficiencies, to observe the length of time during which high protein administration must be continued to restore normal protein equilibrium, and finally to correlate, if possible, the clinical and metabolic status of these patients.

METHOD

Patients suffering from chronic idiopathic ulcerative colitis admitted to the wards of the Gastrointestinal Service of the Graduate Hospital from November 1, 1946 to October 1, 1947, were the subjects of this survey. In

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† American College of Physicians Research Fellow in Internal Medicine.

an effort to make this study as comprehensive as possible no patient who met our requirements was omitted.

Only patients whose diagnoses were proved beyond reasonable doubt were studied. Patients suffering from concomitant metabolic disorders (such as diabetes, nephritis, and hepatitis) were excluded. Only patients who could coöperate in the collection of specimens were accepted. Thus some female patients were eliminated who were unable to collect urine and feces separately. Only adults were studied. No patient had had any surgical operation or major infectious illness within three months of the time of our study. Both of these events are known to affect nitrogen metabolism profoundly.[5] In order to avoid the pitfalls of short-term balance experiments it was necessary that whenever possible our subjects be hospitalized for a considerable period. Both ambulatory and bed patients were used. At times certain patients were febrile; this fact is noted in the protocols. No patient was studied at the time of menstruation, when pregnant or when congestive heart failure was evident. Many patients were anemic and underweight but appeared to be in fluid balance at the time of study.

All diets and refusals were weighed so that the net intake could be computed. Because of the long duration of many of the experiments (and the fickle appetite of the average patient with gastrointestinal disease), identical diets were not used. Free choice of food was allowed within the prescription of the attending physician. Standard dietetic tables were then used to compute the protein, carbohydrate, fat and caloric content of the food actually consumed. Previous studies indicated a maximum of 10 per cent variation between values for nitrogen calculated from the tables and values actually determined by analysis of food. Similar studies for fat indicated a maximum variation of 5 per cent. The value for protein in grams was divided by 6.25 to obtain the weight of equivalent nitrogen in grams. Although this factor assumes a constant nitrogen content of protein it is generally regarded as introducing little error when applied to mixed diets. Nitrogen given parenterally as protein hydrolysate or blood or plasma was added to the oral intake. In this instance the value for the total nitrogen content was used rather than that for free amino nitrogen. Many patients received supplementary feedings of a formula rich in carbohydrate and whole protein. No protein hydrolysate was given orally.

Daily measurement of fluid intake and output and frequent determination of the hematocrit and red blood cell count were done to note any significant diuresis or water storage, with the consequent temporary distortion of nitrogen distribution. Unfortunately blood volume studies were not possible.

The total nitrogen intake and the total urinary nitrogen output were calculated daily. Stool specimens were pooled for a period of several days and the total nitrogen content measured and divided by the number of days to give an average daily stool nitrogen value. The nitrogen balance was then determined by adding the daily stool nitrogen weight to that of urinary

nitrogen and comparing this total to the weight of total nitrogen consumed. The nitrogen loss in sweat (found to be as high as 0.9 gm. per day in profuse perspiration by Bost and Borgstrom[6]) was ignored. Vomitus was analyzed separately and added to the nitrogen excretion. None of our patients produced any measurable amount of sputum.

All nitrogen determinations were made by the macro Kjeldahl method.

All urine was saved and at 7 a.m. each day the pooled urine passed during the previous 24 hours was measured and analyzed for nitrogen. The total stool passed was saved in an air-tight glass jar. Such specimens were pooled over a period of several days, then thoroughly homogenized with a mechanical stirrer after the addition of a suitable amount of distilled water. An aliquot was weighed and its nitrogen content measured. Thirty milliliters of concentrated hydrochloric acid were added to each urine, stool and vomitus container before any specimens were placed in them. The strongly acid medium prevented the loss of nitrogen as ammonia and retarded or prevented bacterial growth. All analyses reported in this study were done in duplicate.

Short term nitrogen balance studies may lead to erroneous conclusions. Even in the normal individual sudden increase or decrease in nitrogen intake is not immediately followed by a corresponding increase or decrease in urinary nitrogen. There is a lag of several days before the intake and output become balanced again at the new level of nitrogen turnover. Cuthbertson and his fellow workers[7] have shown that the addition of a liter of milk daily to an adequate diet given to a normal individual produced a definitely positive nitrogen balance for a period as long as 15 days. Accordingly, the duration of each study was as long as possible, several patients were studied repeatedly and a report of the quantity and quality of the diet for the month preceding the study was obtained from each patient.

Results

The findings in each patient are presented separately, and the clinical status of each is outlined briefly. The daily metabolic data including nitrogen balance are then presented in tabular form and finally any conclusions suggested by the individual study are noted. Additional laboratory examinations not directly concerned with the balance study are reported in the protocols.

Case 1. Male, age 24 years. The patient was admitted to the hospital July 14, 1947. He gave a history of an acute episode of hourly watery bowel movements with streaks of blood lasting one week, two years before entry. He was asymptomatic for one year when these symptoms recurred. A diagnosis of ulcerative colitis was then made by sigmoidoscopy. Roentgen-ray examination of the entire gastrointestinal tract was negative. He lost 20 pounds of weight. After prolonged hospitalization elsewhere, his symptoms gradually subsided, and he was discharged six months before admission to this hospital. He had regained his normal weight by that time. He was well until two months before entry when he had another recurrence,

passing four to six soft blood-streaked stools daily. Since then he lost nine pounds of weight, from a normal of 175 pounds, despite a good appetite. His height was 70 inches. He claimed to have eaten adequately during this period and a review of his diet for the month preceding admission indicated a protein intake of at least 70 grams, and a caloric intake of at least 2500.

Physical examination revealed a well nourished man with no abnormality other than a non-tender, palpable sigmoid colon. Sigmoidoscopy to a depth of eight inches showed a boggy membrane, easily traumatized, with a few scattered, punctate ulcers indicative of chronic ulcerative colitis of moderate activity with no polypoid changes. The urine was normal. The benzidine test for blood in the feces was strongly positive. Dysentery agglutinations were negative. Leukocyte counts and the differential cell count were normal. The sedimentation rate was 8 millimeters per hour (Westergren). The prothrombin time was 15 seconds or 75 per cent of normal concentration. Liver flocculation tests (cephalin-cholesterol, thymol and colloidal gold tests) were negative. The bromsulfalein dye retention test was normal. The van den Bergh test was negative. A fractional gastric analysis showed no free acid in the fasting specimen, hypoacidity and hypermotility. The Frei test was negative.

The roentgen-ray examination showed extensive ulcerative colitis in the distal transverse colon, descending colon and sigmoid without any spasticity or gross deformity of the colon. The esophagus, stomach and duodenum were normal. There was an occasional small bowel loop which appeared slightly distended or dilated. There was also slight segmentation in the small bowel.

During the first week after admission to the hospital there was a low grade fever rising to 100° F. but the patient was afebrile for four days preceding and during the test period. He was treated with a bland diet, bed rest, antispasmodics and ferrous sulfate. His weight on admission was 164.5 pounds and it rose to 168 at the time of discharge. During the test there was a decrease in the frequency of stools.

Comment: The metabolic survey is summarized in table 1a. Despite the small weight loss sustained by the patient, his good appetite, the history of nearly adequate diet and the appearance of being well-nourished, the nitrogen balance survey indicated a protein deficiency which was being corrected by a moderate protein intake during this test. The consistently low urine nitrogen values and the consistently positive nitrogen balance demonstrated a state of previous protein depletion. The stool nitrogen value was at the upper limits of normal.

Course between surveys: The patient was discharged on July 30, 1947. During the next two months he enjoyed good health. Because of the protein deficiency he was given a formula containing 90 gm. of calcium caseinate (containing 88 per cent protein) and 80 gm. of carbohydrate in a quart of milk. This, when taken with his regular high protein, low fat bland diet, provided 185 gm. of protein, about 100 gm. of fat and approximately 2500 calories. He also took one multi-vitamin capsule daily. His bowel movements decreased to an average of one every day. This was formed and passed without urgency, abdominal cramps, blood, pus or mucus. During the first month after his discharge he regained seven pounds of weight to return to his normal weight of 175 pounds. He was entirely asymptomatic. His nitrogen balance was then determined at home, approximately two months after the first study. The results are presented in table 1b.

Comment: Despite the fact that the patient had been taking a high protein diet (about 185 gm. daily) for the previous two month period, he was still storing nitrogen as indicated by the markedly positive nitrogen

TABLE Ia

Male, age 24. Chronic Idiopathic Ulcerative Colitis

Date	Intake				Output					Max. Temp. in °F.	Nitrogen Balance in Grams	Blood Examinations							Date
	Diet Nitrogen in Grams per Day	Diet Fat in Grams per Day	Diet Calories per Day	Fluid Intake, Ml. per Day	Urine Vol. in Ml. per Day	Urine Nitrogen in Grams per Day	Stool Wt. Total in Grams	No. of B.M.'s Daily	Stool Nitrogen in Grams per Day			RBC Count	Hb. in Grams	Hematocrit	Serum Protein in Grams %	Serum Albumin in Grams %	Serum Globulin in Grams %	Blood Urea Nitrogen in Mg. %	
From 7/14 through 7/22 average diet of 13.0 grams N, 90 grams of fat and 2200 calories																			
7/14								7		100		4,570,000	13.5	40	5.84	3.32	2.52	10	7/14
7/23	12.6	97.5	2141	2435	2090	5.85	1406	4	2.53	98.4	+4.2	4,500,000	13.0	40	6.80	3.98	2.82	13	7/23
7/24	12.6	91.1	2065	2020	1358	6.06	Soft, brown	5	2.53	98.6	+4.0								7/24
7/25	13.0	71.1	2073	2175	1450	8.13	semi-liquid	3	2.53	98.0	+2.3								7/25
7/26	11.9	58.9	1883	2480	1670	6.95	stool with	2	2.53	98.3	+2.4								7/26
7/27	17.1	83.3	2207	2350	1972	6.74	some blood,	2	2.53	98.6	+7.8								7/27
7/28	15.0	87.3	1899	2500	1955	8.15	mucus, little pus.	2	2.53	98.6	+4.0	4,510,000	13.2	41	6.79	3.82	2.97	12	7/28
From 7/29 through 9/24 average diet of 29 grams of N, and 2500 calories																			

TABLE Ib

Same patient. Two months later

9/25	29.9	88.0	2571	2640	1875	19.1	479	2	0.94	98.4	+9.9								9/25
9/26	29.7	103.2	2601	2400	1710	21.7	Formed	2	0.94	98.6	+7.1								9/26
9/27	29.8	138.0	2685	2260	1818	22.4	stool. No pus, blood or mucus.	2	0.94	98.2	+6.5								9/27

TABLE Ic

Same patient. One month later

From 9/27 through 10/24 average diet of 29 grams of N, and 2500 calories																			
10/25	28.7	200.9	3795	2040	1255	17.1	232	2	2.49	98.2	+9.1								10/25
10/26	21.3	124.3	2902	1810	1130	17.1	Formed	1	2.49	98.3	+1.7								10/26
10/27	25.6	154.6	3344	2280	1045	15.4	stool. No pus, blood, or mucus.	2	2.49	98.6	+7.7								10/27

balance. The urine nitrogen was considerably greater than in the previous survey but nevertheless about one-fourth of the high dietary nitrogen was being stored. The stool nitrogen on the other hand had returned to a normal value.

Course between surveys: The patient continued on the same high protein and high calorie bland diet inasmuch as he was still deficient in protein. He remained asymptomatic. He had normal bowel movements once or twice daily. His weight remained 175 pounds. His balance was again determined at home one month after the second study. The results are presented in table 1c.

Comment: Despite an unfortunate decline in the dietary intake on October 26 the survey demonstrates that the patient was still storing nitrogen in significant amounts. The proportion of intake being stored was about the same as in the previous survey. It is of interest (and thus far unexplained) that the patient's weight was not increasing coincidentally with the storage of protein.

Case 2. Male, age 39 years. This patient was admitted to the hospital on May 14, 1947. Symptoms of idiopathic chronic ulcerative colitis had been present without interruption for three years. He had experienced a sudden onset of diarrhea with as many as 14 stools a day. There was some blood-streaking of the stool but no gross bleeding. He suffered great urgency and severe cramps in the lower abdomen just before defecation. His appetite was excellent and in reviewing his diet it was estimated that he consumed about 85 gm. of protein and 2800 calories daily during the three months prior to admission. He had lost only 10 pounds of weight during the entire three years. He had a low grade fever intermittently and had had long courses of sulfadiazine, sulfathalidine and sulfaguanidine without improvement.

Physical examination revealed a healthy appearing, well-nourished man. His weight was 180 pounds and his height five feet nine inches. The only abnormal physical finding was the picture of moderately advanced chronic idiopathic ulcerative colitis and a benign rectal polyp seen on sigmoidoscopy.

Laboratory examination showed a sedimentation rate of 59 millimeters per hour, a normal bromsulfalein dye retention test, a normal leukocyte count and a normal differential cell count. His urine was negative and his stools gave a positive benzidine test for occult blood and contained some mucus but little pus.

The roentgen-ray examination showed the chest, esophagus, stomach, duodenum and small bowel to be normal. A barium enema showed extensive ulcerative colitis of the transverse, descending and sigmoid colon. There was no evidence of polyp formation.

His course in the hospital was afebrile. He was given a bland, high protein diet as indicated in table 3. Supplementary vitamins included 12 gm. of brewer's yeast, 100 milligrams of ascorbic acid and one halibut and viosterol capsule daily. He received 6 gm. of sulfathalidine daily. Protein hydrolysate was given intravenously in the form of 50 gm. of Amigen and 50 gm. of glucose each in a 5 per cent solution on the days indicated in the table. On this regimen he noted the gradual disappearance of urgency and cramps as well as blood-streaking of the stools. Some mucus persisted in his feces, but the number of daily movements had decreased to three at the time of his discharge. His discharge weight was 183 pounds or three pounds more than his admission weight. His first survey is reported in table 2a.

Comment: This patient showed a rather large positive nitrogen balance throughout the test indicating a state of protein deficiency despite the rela-

TABLE IIa

Male, age 39. Chronic Idiopathic Ulcerative Colitis

Date	Intake: Diet Nitrogen in Grams per Day	Diet Fat in Grams per Day	Diet Calories per Day	Parenteral Nitrogen in Grams per Day	Fluid Intake, Ml. per Day	Output: Urine Vol. in Ml. per Day	Urine Nitrogen in Grams per Day	Stool Wt. Total in Grams	No. of B.M.'s Daily	Stool Nitrogen in Grams per Day	Max. Temp. in °F.	Nitrogen Balance in Grams	Blood Examinations: RBC Count	Hb. in Grams	Hematocrit	Serum Protein in Grams %	Serum Albumin in Grams %	Serum Globulin in Grams %	Blood Urea N in Mg %	Date
5/15									8		98.4		4,680,000	13.5	43	8.24	4.25	3.99	17	5/15
5/16	26.4	89.3	2853	0	1580	1175	14.35	1644	7	1.93	98.6	+ 8.1								5/16
5/17	27.8	90.9	3114	0	1610	765	10.58	Liquid stool.	7	1.93	98.0	+15.3								5/17
5/18	23.2	101.4	2444	0	1860	1050	14.02	Little pus,	6	1.93	98.4	+ 7.3								5/18
5/19	17.4	87.7	1921	0	1660	740	10.72	some mucus,	4	1.93	98.2	+ 4.8								5/19
5/20	16.1	98.4	2236	0	1560	715	10.31	rare blood	6	1.93	98.6	+ 4.9								5/20
5/21	15.0	70.3	1720	0	1050	835	10.52	streaking.	5	1.93	98.6	+ 2.6								5/21
5/22									4		98.4		4,720,000	14.0	45	6.88	4.25	2.63	14	5/22
From 5/22 through 6/4 average diet of 18 grams of N, 90 grams of fat and 2500 calories. No parenteral N given during this period																				
6/4									4		98.6		4,400,000	13.7	42	6.09	4.25	1.84	13	6/4
6/5	18.8	94.2	2527	6*	2800	1464	9.88	1233	3	2.34	98.4	+12.6								6/5
6/6	17.5	82.1	2200	0	1820	864	5.38	Liquid stool	2	2.34	98.6	+ 9.8								6/6
6/7	14.6	84.9	2261	6*	2810	2010	4.84	No blood or	3	2.34	98.4	+13.4								6/7
6/8	18.8	101.9	2669	6*	2640	2010	12.95	pus, little	3	2.34	98.2	+ 8.5								6/8
6/9	13.0	76.0	2113	6*	2440	1535	7.22	mucus.	3	2.34	98.6	+ 9.4	4,500,000	14.0	43	6.45	4.30	2.15	14	6/9
From 6/10 through 9/19 approximate diet of 30 grams of N, 100 grams of fat and 2500 calories																				

TABLE IIb

Same patient. About three and one-third months later

9/20	30.0	129	2629	0	2950	1575	22.55	480	2	2.90	98.2	+ 4.5								9/20
9/21	30.0	99	2641	0	3240	1875	21.00	Soft, mushy	2	2.90	98.6	+ 6.1								9/21
9/22	30.0	97	2373	0	2040	1000	18.65	stool. No blood, pus or mucus.	2	2.90	98.4	+ 8.4								9/22

TABLE IIc

Same patient. About one month later

From 9/23 through 10/24 approximate diet of 19 grams of N, 125 grams of fat and 2500 calories																				
10/25	20.0	158.5	2734	0	1160	1050	20.00	295	2	2.39	98.4	− 2.4								10/25
10/26	17.6	119.0	2323	0	1620	1110	18.45	Soft, mushy	2	2.39	98.6	− 3.2								10/26
10/27	16.4	110.0	2043	0	1428	930	16.60	stool. No blood, pus, mucus	2	2.39	98.4	− 2.5								10/27

* In form of "Amigen."

tive absence of clinical signs of nutritional deficit. The protein hydrolysate given intravenously in the latter part of the survey seemed to be utilized fairly effectively as indicated by a somewhat greater positive nitrogen balance during this time as compared with the preceding days when no intravenous hydrolysate was given. Comparison is difficult, however, because of variation in diet protein and fluid intake and output. It is of interest that the fecal nitrogen actually increased somewhat in the latter part of the survey despite the decrease in the number of stools.

Course between surveys: Following discharge from the hospital the patient continued to do well over the three and a third month period until the second survey was done. During this time he was consuming about 190 gm. of protein, 100 gm. of fat and 2500 calories daily. These figures included a formula containing 80 gm. of calcium caseinate (containing 88 per cent protein) and 80 gm. of carbohydrate in a quart of milk. The number of stools gradually decreased to two daily and were formed but soft. The patient was asymptomatic and returned to work. A benign rectal polyp was fulgurated through the proctoscope. Despite the ample diet the patient had gained only three pounds to reach his normal weight of 180 pounds. The second survey conducted at the patient's home is reported in table 2b.

Comment: The moderately high positive balance recorded for the three days is significant. It is suggested that the patient is still storing nitrogen after three and a third months of the high protein regimen. It is interesting that the fecal nitrogen is somewhat higher than during the first survey. The failure to gain weight corresponding to the nitrogen storage is unexplained.

Course between surveys: Due to a misunderstanding the patient reduced the protein content of his formula just after the second survey. For the next month his daily protein intake approximated 120 gm. or 19 gm. of nitrogen. He continued to be asymptomatic and the stools were formed but soft as before. His weight remained constant. One month after the second survey a third was made. It is summarized in table 2c.

Comment: The patient was in nitrogen balance during this test. The slight negative balance recorded is probably not significant at this high level of nitrogen intake. Had the previous daily intake of 30 gm. of nitrogen been maintained it is, of course, possible that the patient would still have been in positive balance.

Case 3. Male, age 31 years. The patient gave a history of chronic idiopathic ulcerative colitis of eight months' duration. During the first four months of his illness he suffered from diarrhea, consisting of five watery stools daily without blood, pus or mucus. Four months before entry he began to lose weight progressively and at the time of admission he weighed 147 pounds. His usual weight had been 177, and his height was 69 inches. He complained of generalized malaise and periodic epigastric pain which eventually gave way to crampy low abdominal pain. His appetite and food intake remained good. A review of his dietary habits showed a minimum intake of 100 gm. of protein and 3000 calories daily during his illness. His diarrhea became worse and two months before entry he was having 15 movements daily. Mucus and flecks of blood began to appear in his stools.

Physical examination showed a well-developed and nourished individual who did not appear ill. The only abnormal findings were generalized tenderness of the ab-

domen, increased peristalsis, a moderately spastic rectal sphincter and a rectal mucosa which felt granular on palpation. Sigmoidoscopy revealed a thin layer of purulent exudate covering the entire mucosa of the rectum and lower sigmoid colon. Under this exudate were many pin-point ulcerations and the mucosa was easily traumatized. The bowel wall was stiff and the lumen somewhat narrowed.

Laboratory examination showed the leukocyte count to be 9600 with a normal differential count. The urine was negative. The sedimentation rate was 34 millimeters per hour and the prothrombin time 13 seconds or 100 per cent concentration of prothrombin. The stool examination indicated the presence of some mucus, much pus and a small amount of blood. Thymol and cephalin-cholesterol flocculation tests were negative and the bromsulfalein dye retention test was normal. A fractional gastric analysis was normal.

His course in the hospital was afebrile. Treatment included a bland high protein diet as indicated in table 5. Treatment with sulfadiazine (6 gm. daily) and penicillin (600,000 units daily) was begun on January 8 but was stopped after two days because of the development of conjunctivitis. He received two multi-vitamin capsules daily. He was ambulatory throughout his hospitalization. His weight did not vary significantly from 147 pounds during his stay. On admission his bowel movements had numbered nine per day but had decreased to three at the time of discharge, when he was asymptomatic except for low abdominal cramps preceding and relieved by each bowel movement.

The roentgen-ray examination showed the chest, esophagus, stomach and duodenum to be normal. Examination of the small intestines showed slight segmentation with some coarsening of the mucosal pattern probably indicative of a slight degree of disturbed motor physiology secondary to the nutritional deficiency of the patient. Barium enema revealed the entire colon to be moderately narrowed and tubular in configuration with irregular and indistinct margins most probably due to chronic ulceration and scarring from ulcerative colitis.

Comment: The patient's metabolic survey is reported in table 3. This patient showed a consistently positive nitrogen balance indicating a protein deficiency in spite of the fact that he appeared well nourished and that it might have been surmised that his history of weight loss involved primarily a loss of fat. The rather low urine nitrogen indicates that the protein deficit was probably of long standing. The stool nitrogen value was quite high, an observation that may be correlated with the predominantly purulent character of the feces. The increase in the serum protein concentration was due primarily to an increase in the globulin fraction.

Case 4. Male, age 47 years. The patient gave a history of two episodes of chronic idiopathic ulcerative colitis. The first episode of diarrhea occurred two years before admission and lasted six weeks. He had 10 to 15 stools per day containing gross blood. He recovered and was entirely asymptomatic, eating everything and maintaining his normal weight of 138 pounds until six weeks before admission when the second episode of rectal bleeding took place. Two weeks later his diarrhea returned, consisting of 10 to 15 movements daily with blood-streaking. He was put on a bland diet emphasizing albumin water, pureed vegetables and liquids. He took only liquids for the five days preceding admission. He lost 15 pounds in the six weeks before hospitalization. A review of his diet for the month before entry indicated a maximum daily protein intake of 30 gm. and a caloric intake of 2700.

Physical examination showed an undernourished, pale, lethargic man who appeared chronically ill. His height measured 69 inches. There was generalized abdominal tenderness. The rectal mucosa was tender and granular to the touch. No

TABLE III

Male, age 31. Chronic Idiopathic Ulcerative Colitis

Date	Intake				Output					Max. Temp. in °F.	Nitrogen Balance in Grams	Blood Examinations							Date
	Diet Nitrogen in Grams per Day	Diet Fat in Grams per Day	Diet Calories per Day	Fluid Intake, Ml. per Day	Urine Vol. in Ml. per Day	Urine Nitrogen in Grams per Day	Stool Weight Total in Grams	No. of B.M.'s Daily	Stool Nitrogen in Grams per Day			RBC Count	Hb. in Grams	Hematocrit	Serum Protein in Grams %	Serum Albumin in Grams %	Serum Globulin in Grams %	Blood Urea Nitrogen in Mg. %	
1/21	12.45	55	2200	1450	530	5.50	2207, Mucoid, purulent, bloody stool	9	7.60	98.6	−0.65	4,490,000	13.0	40	6.56	4.12	2.44	9	1/21
1/22	18.72	89	2540	1505	650	5.71		9	7.60	98.4	+5.41								1/22
1/23	21.67	99.6	2810	1742	785	5.50	2141	8	8.3	98.2	+7.87								1/23
1/24	21.75	100	2905	1710	1260	6.51	As above	7	8.3	98.6	+6.94								1/24
1/25	22.00	100	3005	2040	1740	5.93	4030	6	7.85	98.6	+8.22								1/25
1/26	21.85	100	3045	1745	945	5.62	As above	6	7.85	98.0	+8.38								1/26
1/27	21.50	100	2895	1520	605	5.50		4	7.85	98.4	+8.15								1/27
1/28	20.80	98	2844	1732	1100	5.74		3	7.85	98.8	+7.21								1/28
1/29								3		98.1		4,500,000	13.0	40	7.60	4.32	3.28	10	1/29

blood was noted during the rectal examination. No further abnormality was noted on physical examination. Sigmoidoscopy showed the lumen of the bowel to be contracted with obliteration of the second and third valves. There were many polypoid projections from the mucosa, 1 to 2 mm. high. Traumatizing the mucosa produced very little bleeding and the general impression was that of healing.

Laboratory examination revealed a normal leukocyte count and differential count, negative dysentery agglutinations, negative cephalin-cholesterol and thymol flocculation tests. The sedimentation rate was 55 mm. per hour. The urine was negative. Stool examination revealed some mucus, little pus and no gross blood. On admission a positive benzidine test for occult blood was present which became and remained negative two weeks after admission on March 15.

His course in the hospital was prolonged but ultimately satisfactory. He was encouraged to eat a bland, high protein diet which was supplemented from the outset by the administration of a formula consisting of 100 gm. of skim milk powder and 100 gm. of carbohydrate in 1000 ml. of skim milk and protein hydrolysate given intravenously. Unfortunately there were a number of days when his oral intake of food was quite low due to severe anorexia during the early days of the survey. He was kept in bed. During the first week of hospitalization he had a daily temperature rise to 102° F. but by the time the first survey was begun two weeks later he was afebrile and remained so throughout this admission. He received 6 gm. of sulfadiazine daily from March 1 to March 16, and 25,000 units of penicillin every three hours from March 16 to March 29. Throughout his stay he received 1 ml. of crude liver intramuscularly daily. Orally he received daily one halibut and viosterol capsule, 1 gm. of ferrous sulfate dissolved in an aqueous vehicle, 10 gm. of brewer's yeast and one multivitamin capsule. His weight on admission was 110 pounds and on discharge 120. At the time of discharge he was asymptomatic, having four formed bowel movements daily.

The roentgen-ray examination showed the chest, esophagus, stomach and duodenum to be normal. Examination of the small intestine showed a slight degree of distortion of motor physiology. There was no evidence of involvement of the terminal or distal ileum by the process which involved the large bowel. Barium enema revealed the entire colon to be involved in a narrowing, stiffening process with loss of normal configuration, extensive pseudopolypoid changes and marked irritability. The general picture was consistent with the diagnosis of chronic ulcerative colitis.

Comment: The patient's metabolic survey is shown in table 4a. As might be deduced from the clinical history of this patient there was a considerable deficiency of protein as indicated by the consistently diminished urine nitrogen excretion despite a high nitrogen intake. It will be noted that as the intake of nitrogen gradually increased over the five week period there was a corresponding but smaller increase in urine nitrogen so that the positive nitrogen balance tended to become greater in the latter part of the month.

Despite the hazards of interpreting the extent of utilization of parenterally administered protein hydrolysate on the basis of short nitrogen balance studies, we may be permitted to offer tentative conclusions on this question. During the first six days there appeared to be rather complete utilization of the parenteral nitrogen. With the exception of the increase in urine nitrogen on March 14 (associated with a mild diuresis) the excretion of nitrogen in the urine did not seem to be increased by the extra nitrogen given parenterally. If the data from March 27 through April 4 are inspected and if the total nitrogen intake for each day (the sum of diet and parenteral nitrogen)

TABLE IVa

Male, age 47. Chronic Idiopathic Ulcerative Colitis

Date	Intake					Output					Max. Temp. in °F.	Nitrogen Balance in Grams	Blood Examinations							Date
	Diet Nitrogen in Grams per Day	Parenteral Nitrogen in Grams per Day	Diet Calories per Day	Fluid Intake, Ml. per Day	Diet Fat in Grams per Day	Urine Vol. in Ml. per Day	Urine Nitrogen in Grams per Day	Stool Wt. Total in Grams	No. of B.M.'s Daily	Stool Nitrogen in Grams per Day			RBC Count	Hb. in Grams	Hematocrit	Serum Protein in Grams %	Serum Albumin in Grams %	Serum Globulin in Grams %	Blood Urea N in Mg. %	
From 3/1 through 3/10 average diet of 14 grams of N, 50 grams of fat and 2500 calories, as well as 6 grams of parenteral nitrogen on alternate days																				
3/3									14		103.0		3,400,000	9.5	30	4.92	2.72	2.24	7	3/3
3/11	6.0	0	1077	1790	18.5	1125	7.08	1567	9	2.40	99.0	− 3.48	4,200,000	12.0	38	5.28	2.59	2.69	8	3/11
3/12	14.7	6*	2215	2200	51.0	1520	7.59	Liquid,	8	2.40	98.6	+10.71								3/12
3/13	14.0	6*	2273	2420	49.0	1130	7.14	brown;	8	2.40	98.8	+10.46								3/13
3/14	16.8	6*	2301	1670	42.5	1952	11.92	slight mucus	7	2.40	98.6	+ 8.48								3/14
3/15	14.8	0	1674	1955	44.5	1050	7.92	and moder-	7	2.40	98.4	+ 4.48								3/15
3/16	15.1	0	1644	2170	28.5	743	7.14	ate pus.	6	2.40	98.6	+ 5.56								3/16
From 3/17 through 3/26 average diet of 16 grams of N, 45 grams of fat and 1800 calories, as well as 6 grams of parenteral nitrogen on alternate days																				
3/18									6		98.2		3,600,000	10.0	31	4.80	3.19	1.61	14	3/18
3/27	18.3	0	2354	2150	46.7	1520	7.72	3555	6	3.20	98.0	+ 7.4	3,600,000	10.0	34	4.80	2.86	1.94	14	3/27
3/28	24.8	7.2x	2651	2480	46.7	1865	9.58	Formed,	5	3.20	98.2	+19.2								3/28
3/29	19.3	0	2434	2590	59.1	2605	10.92	mucoid	4	3.20	98.1	+ 5.2								3/29
3/30	23.4	6.*	2659	2630	48.1	2630	10.24	brown stool.	4	3.20	98.6	+15.9								3/30
3/31	22.9	0	2599	2490	48.6	1655	8.25	No food,	4	3.20	98.4	+11.4								3/31
4/1	18.2	7.2x	2504	2660	52.5	2710	13.00	little pus,	4	3.20	98.0	+ 9.2	3,600,000	10.0	34	4.80	3.32	1.48	12	4/1
4/2	23.4	0	2547	2660	52.5	1694	8.29	no blood.	5	3.20	97.6	+11.9								4/2
4/3	21.2	7.2x	2149	2670	54.5	2210	12.41		4	3.20	98.0	+12.8								4/3
4/4	23.5	0	2187	2530	49.5	1685	9.11		4	3.20	98.2	+11.2								4/4
From 4/5 through 4/11 average diet of 22 grams of N, 60 grams of fat and 2200 calories, as well as 7.2 grams of parenteral nitrogen on alternate days																				
4/12	24.6	7.2x	2785	3165	63.9	3280	12.92	3594	5	4.43	98.0	+14.4								4/12
4/13	21.4	0	3137	3105	94.7	2340	11.70	Formed,	4	4.43	97.6	+ 5.3								4/13
4/14	26.6	7.2x	3290	3300	78.5	3194	12.88	mucoid	3	4.43	98.2	+16.5								4/14
4/15	26.7	0	3273	3105	86.7	1975	10.92	brown stool.	4	4.43	98.6	+11.4	4,280,000	12.0	38	6.24	3.72	2.52	10	4/15
4/16	25.8	7.2x	3230	3180	73.0	2845	12.22	No food,	4	4.43	98.4	+16.4								4/16
4/17	25.9	(0 Nitrogen) (1000 ml. 10% Glucose)	3334	3180	66.5	2900	10.62	little pus, no blood.	4	4.43	98.2	+10.9								4/17

* In form of "Amigen."
x In form of "Supprotein."

is compared with the nitrogen balance for that day, it will be seen that variations in the nitrogen intake were accompanied by quantitatively similar variations in the nitrogen balance with the exception of two days—April 1 and April 3. In other words, apart from those two days, added nitrogen (oral and parenteral) was quite well utilized.

In brief, we think it is justifiable to consider that our patient utilized the parenteral nitrogen quite well. However, the interpretation of such day to day variation in nitrogen balance data is very hazardous.

Course between surveys: The patient was discharged from the hospital on April 19. Immediately following discharge the number of his bowel movements increased from four to seven daily. Nevertheless he gained in strength and his weight increased from 120 pounds on discharge to 132 pounds on July 19. During this period he consumed approximately 120 gm. of protein and 3000 calories daily. On June 1 he took a part-time clerical job which he kept until July 19, at which time he began to have anorexia and markedly reduced his food and fluid intake. He lost four pounds in weight between July 19 and July 25. On the latter date he had lower abdominal crampy pain for the first time since discharge and two days later diarrhea returned with a movement every hour. Blood was seen in the stool first on August 1 and each day thereafter until admission on August 9.

On readmission he was markedly wasted and dehydrated. His weight was 117 pounds. His lower abdomen was moderately tender and rectal examination had to be deferred because of a tender anus with inflamed hemorrhoids. There was no definite evidence of vitamin B deficiency.

Laboratory examination revealed a normal urine, leukocyte count and differential leukocyte count. The stool on August 11 gave a strongly positive benzidine test for occult blood and many red and white blood cells were seen on microscopic examination. The benzidine test became negative on September 11 and remained so thereafter. An electrocardiogram was normal. Liver flocculation tests were negative.

His course was more stormy than on the previous admission. At the outset he had temperature elevations daily to approximately 103° F. and hourly bloody bowel movements with lower abdominal crampy pain. He was placed at bed rest and given a bland, high protein, low fat, high calorie diet supplemented by a formula consisting of 80 gm. of skim milk powder and 80 gm. of carbohydrate in 1000 ml. of water as well as blood and protein hydrolysate intravenously. However, as can be seen in table 4b, during the first part of his stay his total dietary intake was often very low despite the most persistent urging. On August 19 the daily intramuscular injection of 20 mg. of thiamin, 10 mg. of niacin and 2 ml. of crude liver extract was begun, as well as the daily oral administration of 100 mg. of ascorbic acid, and three halibut and viosterol capsules. Despite these measures his condition became considerably worse during the first three weeks of his stay. On August 27 his weight was 108 pounds. On September 1 his condition had deteriorated to the point where it was feared that if a remission did not occur a fatality might result. Accordingly, it was decided to institute a "medical ileostomy," as recently used by T. Grier Miller.[4] A Miller-Abbott tube was passed into the distal ileum so that ileal contents could be withdrawn through the tube rather than discharged into the colon. Oral feedings were continued. On this regimen the frequency of bowel movements dropped from 14 per day to 3, but the patient did not tolerate the tube and it had to be withdrawn after three days. The immediate problem seemed to be nutritional and therefore the patient's family was asked to supply additional protein-rich food prepared especially according to the patient's taste. This food was weighed in the same manner as the regular hospital diet. This regimen was begun on September 10 and it can be seen from table 4b that his food intake immedi-

TABLE IVb

Readmission of Same Patient Described in Table IVa

Date	Intake					Output					Max. Temp. in °F.	Nitrogen Balance in Grams	Blood Examinations							Date
	Diet Nitrogen in Grams per Day	Parenteral Nitrogen in Grams per Day	Diet Calories per Day	Fluid Intake, Ml. per Day	Diet Fat in Grams per Day	Urine Vol. in Ml. per Day	Urine Nitrogen in Grams per Day	Stool Wt. Total in Grams	No. of B.M.'s Daily	Stool Nitrogen in Grams per Day			RBC Count	Hb. in Grams	Hematocrit	Serum Protein in Grams %	Serum Albumin in Grams %	Serum Globulin in Grams %	Blood Urea N in Mg. %	
8/11	3.26	6*	1061	2050	27	805	10.71	1563	24	1.61	103.0	− 3.1	3,999,000	11.5	34	5.36	3.25	2.11	15	8/11
8/12	14.20	0	1524	1690	66.1	385	5.65	Liquid with	21	1.61	102.8	+ 7.0								8/12
8/13	9.07	6*	2052	2760	59.5	552	6.28	pus, blood,	22	1.61	103.0	+ 7.1								8/13
8/14	8.00	0	1265	2100	38.0	395	5.85	and mucus	24	1.61	102.5	+ 0.6								8/14
8/15	5.74	10.8#	1579	4000	29.1	590	10.80	in small	22	1.61	101.8	+ 4.1								8/15
8/16	5.64	0.6#	923	2150	31.8	810	12.96	amounts	20	1.61	103.1	− 8.4								8/16
8/17	4.57	0	1053	1700	38.1	280	5.44		18	1.61	102.2	− 2.4								8/17
8/18	8.16	14.4x	1943	3500	47.4	1500	18.81		17	1.61	102.0	+ 2.2								8/18
8/19	6.40	7.2x	1745	2600	46.2	1400	12.05		18	1.61	102.2	0								8/19
8/20	6.56	14.4x	1600	3200	47.0	1658	17.71		15	1.61	101.9	+ 1.7								8/20
8/21	3.33	14.4x	1358	3400	47.4	1712	15.85	499	15	1.09	102.2	+ 0.9								8/21
8/22	4.67	14.4x	1260	2400	47.4	1121	11.10	As above	14	1.09	101.2	+ 7.0								8/22
8/23	7.75	14.4x	1740	3400	75.1	1520	15.60		12	1.09	100.8	+ 5.6								8/23
8/24	7.00	14.4x	1760	2200	51.7	968	11.09		12	1.09	102.0	+ 9.4	3,260,000	9.0	29	5.06	3.02	2.04	12	8/24
From 8/25 through 9/8 average diet of 8 grams of N, 60 grams of fat and 1600 calories, as well as 14.4 grams of parenteral N daily																				
9/9	10.2	0	1929	1760	98.8	1240	8.70	1420	10	3.05	101.0	− 1.5								9/9
9/10	17.3	0	2739	2160	107.7	1320	9.01	Soft brown,	10	3.05	100.2	+ 5.3	3,400,000	9.5	32	7.20	3.98	3.22	14	9/10
9/11	33.9	0	3382	2330	149.7	1700	11.50	slightly	10	3.05	101.0	+19.4								9/11
9/12	25.5	0	3011	2220	122.9	1388	4.37	mucoid. No	10	3.05	100.8	+18.1								9/12
9/13	20.0	0	3100	2390	112.4	1640	4.05	blood, pus.	10	3.05	99.7	+13.0								9/13
9/14	15.6	16*	2238	3760	112.9	2970	14.35	1267	10	1.60	99.2	+15.6								9/14
9/15	17.0	0	2879	1910	168.4	970	14.12	Soft brown,	12	1.60	98.6	+ 1.3								9/15
9/16	17.0	8*	2583	2830	170.8	1935	15.40	slightly	12	1.60	99.4	+ 8.0								9/16
9/17	23.7	0	3573	1860	219.1	1245	13.38	mucoid. No	10	1.60	99.8	+ 8.7								9/17
9/18	21.2	8	2871	2300	126.8	2000	16.40	blood or pus.	10	1.60	99.4	+11.2								9/18
9/19	18.8	0	3016	2367	144.4	—	—	Occ. food particle.	10	1.60	99.8	—	3,900,000	10.0	35	7.10	4.20	2.90	13	9/19

* In form of "Amigen."
\# In form of blood.
x In form of "Supprotein."

ately rose and from that day hence clinical improvement was steady. Except for the increased frequency of stools and the low-grade fever he was completely asymptomatic at the end of the survey nine days later. Neither chemotherapy nor antibiotics were given during this admission.

Comment: The second metabolic survey is presented in table 4b. During the first week of the survey the fluid intake was insufficient, in view of the fever and diarrhea, to insure an adequate urine volume. This fact may account for the low urine nitrogen during the first week. The parenteral nitrogen given from August 18 through August 24 enabled the patient to remain in slight positive balance despite the low oral intake, diarrhea and fever. The decline in the hematocrit and in the values of the blood constituents between August 11 and August 24 was probably due primarily to restoration of normal blood volume. There was good utilization of the high diet nitrogen ingested on September 10 through September 13 as indicated by a low urine nitrogen excretion and a rather high positive nitrogen balance. It seems important to emphasize that clinical improvement began at this time when the patient began to ingest large quantities of home-cooked food.

Case 5. Male, age 35 years. Eight years before admission this patient developed epigastric pain which recurred over a two year period at the end of which time a roentgen-ray diagnosis of duodenal ulcer was made. He had lost 35 pounds of weight to reach a level of 125. On a rigid ulcer regimen he had good relief of symptoms and his weight increased to 185 pounds five years before entry. Since then he had had no definite recurrence of the epigastric pain. Three and a quarter years before admission he had an attack of diarrhea without blood which subsided completely in a few days. He was normally constipated thereafter, and occasionally after a difficult defecation he would note blood in the stool. One and one-third years before admission he had an operation for anal fissure. Following operation bleeding with defecation was quite frequent. A sigmoidoscopy done four months before admission had shown chronic idiopathic ulcerative colitis. Apart from the bleeding the stools were normal and there were no other symptoms until four weeks before entry when he suffered lower abdominal crampy pain just before defecation and the frequency of bowel movements increased to three or four daily. Two weeks before admission the diarrhea increased to 10 to 15 movements daily with blood. All were watery and were associated with severe crampy abdominal pain only partially relieved by a bowel movement. The two weeks before admission had been spent in bed with no improvement. It was estimated that during the four weeks before entry he consumed no more than 60 gm. of protein and 2000 calories daily. Previously he had taken a normal diet. Three months before admission he weighed 182 pounds, his usual weight. On admission on May 5 he weighed 158 pounds. The patient was highly emotional about his family affairs and suffered considerable psychic tension in his work.

Physical examination indicated some recent weight loss. His height was 68 inches. There was tenderness in the left lower quadrant of the abdomen, but the rectal examination and the remainder of the physical examination were negative. Sigmoidoscopy indicated a moderately active colitic process with considerable bloody and purulent discharge.

Laboratory examination revealed a normal urine. On admission his stool gave a strongly positive benzidine test for occult blood and many red and white blood cells were seen on microscopic examination. The benzidine test remained positive until July 3 after which it was negative. The leukocyte count and differential cell count were normal throughout his stay. The sedimentation rate was 94 on May 15. The

bromsulfalein dye retention test and the liver flocculation tests were normal. The dysentery agglutinations were negative.

His course in the hospital was stormy. His condition gradually deteriorated for the first seven weeks to reach a critical level in the eighth week (the first week in July). During the first six week period he received intensive sulfasuxidine and penicillin without benefit (in fact with decline, as just stated). On June 24 chemotherapy and antibiotics were stopped in view of their failure to relieve the patient's critical condition. His weight at this time was 131 pounds, representing a 27 pound loss since admission. It was therefore decided to direct greater attention to his nutrition. His appetite was poor and the most persistent urging was required to maintain even a moderate dietary intake. On this regimen clinical improvement began to be apparent during the second week of July with some reduction in temperature, pain and diarrhea. During the third week of July the daily maximum temperature elevation averaged 100° F. and the frequency of bowel movements was four daily. At the time of discharge, July 28, his weight was 125 pounds, he was having three bowel movements daily and except for weakness and the low grade fever he was asymptomatic. It was felt that he could convalesce more satisfactorily at home after more than two months in the hospital.

Roentgen-ray examination showed the chest, esophagus, and stomach to be normal. There was moderate deformity of the duodenal cap, the result of scarring from previous ulceration. No evidence of active ulcer was identified. The small intestines were normal. Examination of the colon by means of a barium enema showed an irregular marginal border of the colon extending from the proximal transverse colon to the sigmoid. Increased haustrations of the transverse and upper descending colon were demonstrated. The roentgen picture was that of a chronic ulcerative colitis involving the transverse, descending and sigmoid colon.

Comment: The metabolic survey is reported in table 5. During the period from May 14 through May 19 there was positive nitrogen balance despite the presence of fever and a low calorie intake. This finding demonstrates the existence of protein depletion. There appeared to be good utilization of the parenteral nitrogen. During the second period beginning on June 24 there also appeared to be good utilization of parenteral nitrogen. The low urinary nitrogen values in the latter part of this period indicate that a profound deficiency of protein had existed for some time and that the nitrogen metabolism was operating with great economy, as is, for example, the case in starvation. This is particularly striking when it is recalled that the patient was febrile throughout the entire survey. After June 29 he was dependent primarily upon his oral intake for nitrogen and it can be seen that although this was average in quantity it was grossly inadequate for the patient's needs. Ideally he should probably have continued to receive relatively large amounts of parenteral nitrogen throughout this period. It will be noted that a state of consistent small positive nitrogen balance preceded the clinical improvement by approximately two weeks. The stool nitrogen in this patient was the highest of any of our colitis patients (with the exception of the last period in the first survey of case 4). There was considerable purulent exudate present in these stools which is believed to account in part for their high nitrogen content.

TABLE V

Male, age 35. Chronic Idiopathic Ulcerative Colitis

Date	Intake					Output					Max. Temp. in °F.	Nitrogen Balance in Grams	Blood Examinations							Date
	Diet Nitrogen in Grams per Day	Parenteral Nitrogen in Grams per Day	Diet Calories per Day	Fluid Intake, Ml. per Day	Diet Fat in Grams per Day	Urine Vol. in Ml. per Day	Urine Nitrogen in Grams per Day	Stool Wt. Total in Grams	No. of B.M.'s Daily	Stool Nitrogen in Grams per Day			RBC Count	Hb. in Grams	Hematocrit	Serum Protein in Grams %	Serum Albumin in Grams %	Serum Globulin in Grams %	Blood Urea N in Mg. %	
5/14	7.91	7.2*	1324	1500	37.3	830	11.72	5111	10	5.75	100.8	−2.3								5/14
5/15	10.61	0	1275	2320	49.0	555	7.82	Some	9	5.75	101.2	−2.9	3,700,000	10.5	35	6.40	3.45	2.95	14	5/15
5/16	15.21	7.2*	2088	3440	35.2	840	10.15	mucus; some	10	5.57	101.0	+6.5								5/16
5/17	11.60	7.2*	1707	2980	38.2	950	11.08	blood; much	9	5.75	101.4	+2.0								5/17
5/18	10.95	7.2*	1724	3110	44.3	1045	10.19	pus; liquid	8	5.75	100.8	+2.2								5/18
5/19	17.32	0	2119	2570	47.0	845	9.48	stools	10	5.75	100.6	+2.1	3,850,000	11.0	36	6.35	3.35	3.00	13	5/19
	From 5/20 through 6/23 average diet of 14 grams of N, 45 grams of fat and 2400 calories, as well as 7.2 grams of parenteral nitrogen daily																			
6/24	14.6	13.2#	2670	3140	68.6	1330	13.72	2158	8	5.50	103.4	+8.6	3,700,000	11.0	36	6.96	2.86	4.10	12	6/24
6/25	13.1	9.1#	2450	3500	59.2	1320	15.13	As above	10	5.50	103.6	+1.6								6/25
6/26	12.0	12.0−	2353	3880	50.6	1125	12.21		11	5.50	103.0	+6.3								6/26
6/27	10.6	6.0−	1940	2800	40.6	1115	10.32		12	4.36	103.4	+1.9								6/27
6/28	14.1	0	2516	2455	64.7	1215	8.94		11	4.36	102.8	+0.8								6/28
6/29	19.8	6.0−	2463	2900	82.8	1560	11.91		12	4.36	103.2	+9.5								6/29
6/30	14.6	0	1974	2070	52.9	1015	6.46	7680	13	4.36	103.4	+3.8								6/30
7/1	15.8	3.1#	2146	1870	81.6	1025	6.15	Soft brown;	11	4.36	103.0	+8.4								7/1
7/2	12.5	0	1790	2200	70.0	1658	6.91	some mucus;	12	4.36	104.0	+1.2								7/2
7/3	12.7	0.6#	1735	2600	44.7	1210	6.22	much pus,	13	4.36	104.2	+2.7								7/3
7/4	11.1	3.1#	1662	2200	66.2	1005	6.47	not formed;	12	4.36	103.8	+3.4								7/4
7/5	12.5	3.1#	2100	2520	66.1	910	4.44	little blood	9	4.36	103.8	+6.8								7/5
7/6	6.8	0	1359	1990	41.0	1220	4.86		7	4.36	102.5	−2.4								7/6
7/7	9.7	3.1#	1663	1440	54.3	1325	6.58		6	4.36	102.0	+1.9								7/7
7/8	13.5	3.1#	2077	1830	77.2	740	3.61		6	4.36	101.2	+8.6								7/8
7/9	12.5	0	1893	1570	74.0	1230	5.06		7	4.36	101.4	+3.1								7/9
7/10	12.8	0	2014	1440	75.2	1342	5.23		6	4.36	101.2	+3.2	4,580,000	13.5	43	7.12	3.32	3.80	13	7/10

− In form of "Amigen."
In form of blood.
* In form of "Supprotein."

Discussion

Each of the five individuals studied was found to be deficient in protein as indicated by the presence of a positive nitrogen balance. It is assumed that, in general, the normal adult individual does not store protein and that, under conditions of constant adequate nitrogen intake and cardio-renal competency, the nitrogen excretion is equal to the nitrogen intake; and it is further assumed that, under these same conditions, a positive nitrogen balance is evidence of preëxisting protein deficiency.[8] The existence of protein deficiency cannot be excluded by the absence of physical signs of malnutrition or by the presence of a normal concentration of serum protein. A diet of 70, 85 and 100 gm. of protein before hospitalization in cases 1, 2, and 3 respectively did not prevent a protein deficiency.

All of these patients were readily placed in positive nitrogen balance by the administration of a moderately large amount of protein. There was relatively little increase in urinary nitrogen excretion following increase in nitrogen intake, even in cases 4 and 5 in which the presence of fever might have been expected to increase urine nitrogen. This observation conforms to the pattern of economical utilization of protein found in patients chronically malnourished. On the other hand, patients suffering from acute infections lose large amounts of nitrogen in the urine early in the course of their illness and at this time even large amounts of oral and parenteral protein may not bring about positive nitrogen balance.

It is tempting to presume to assay definitively the utilization of parenterally administered nitrogen by these five patients. The conditions of our study, however, do not permit any final conclusion on this problem. As mentioned previously, Cuthbertson et al.[7] have found it difficult to determine the utilization of added dietary nitrogen in short term balance experiments because of a lag of as long as 15 days in the excretion of extra nitrogen following the addition of extra nitrogen to an adequate diet given to normal individuals. It should be emphasized again that our remarks on the degree of utilization of parenteral nitrogen by the patient described in case 4 are tentative.

The fecal nitrogen value varied considerably. During the period of most active diarrhea it ranged from 1.9 gm. to 8.3 gm. of nitrogen daily. It could not be correlated with the frequency of bowel movement or the severity of the illness. The highest value was found in one of the less ill patients (case 3). We believe abnormal fecal nitrogen in these patients is due to the presence of a purulent exudate and, to a lesser extent, blood, as is shown in the tables. Evidence of incomplete absorption of food was scanty. Gross food particles were observed only in case 4. In general there was no correlation between food and fecal nitrogen values. Measurement of the fecal total fat in these patients (to be reported) showed but a moderate increase (if any) above normal values. These findings are in keeping with the generally accepted belief that the colon is not the major site of absorption of foodstuffs

and that the increased fecal material in patients with colitis represents primarily the inflammatory exudate of the colon itself. Our findings lend no support to the claim that large dietary intakes increase the fecal loss in these patients.

The ultimate clinical course of each of these patients was satisfactory and their condition was improved at the time of discharge from the hospital. Our initial postulate stated that a positive protein balance was a necessary condition for clinical improvement in a patient suffering from chronic ulcerative colitis who was also depleted in protein. If this postulate is correct, then clinical improvement in each of our patients should have been preceded by a period of consistent positive nitrogen balance. Conversely, there should have been no clinical improvement during a period of negative nitrogen balance. Accordingly, the date on which consistent positive nitrogen balance was first achieved was compared with the time of onset of symptomatic relief in each case.

In case 1 the patient first noted definite relief of symptoms on July 25. Positive nitrogen balance was consistent throughout the survey which began on July 23; it is not known when protein storage began. In case 2 the patient began to deposit protein at least one week before clinical improvement was definite. Relief of symptoms and positive nitrogen balance began simultaneously in case 3. During the first admission of case 4 clinical improvement was noted first about four days before the survey in table 4a began. Unfortunately metabolic balance studies were not begun on admission and we do not know when positive nitrogen balance was first obtained. It is probable, however, that he was in positive balance from the outset as his protein intake (orally and parenterally) from March 1 through March 10 approximated that from March 11 through March 16. Therefore it is likely that positive nitrogen balance preceded clinical improvement. On the second admission of this same patient his clinical condition actually deteriorated for the first month of his hospitalization. During this period consistently positive nitrogen balance was not attained. With the great increase in oral intake beginning on September 10, consistent positive balance was achieved and from that date clinical improvement was steady. In case 5 the onset of consistent positive nitrogen balance preceded clinical improvement by about two weeks.

Therefore in the six admissions of these five patients positive nitrogen balance either preceded or coincided with clinical improvement. No clinical improvement was observed during any period of negative balance. It is possible that the demonstration of consistent positive nitrogen balance (in the absence of azotemia) may enable the clinician to predict clinical improvement in a patient critically ill with colitis, or, at least, to be assured that the metabolic stage is set for remission of the disease.

We were interested in the length of time during which the high protein regimen would have to be continued in order to restore depleted protein completely and to attain nitrogen equilibrium. Therefore follow-up nitro-

gen balance studies were done in the two patients who had been the least ill (cases 1 and 2). In case 1, after a daily nitrogen intake of approximately 29 gm. over a period of three months following discharge from the hospital, the protein deficiency had not yet been corrected, as is shown by the positive nitrogen balance. In case 2 the protein intake was similar to that of case 1. Between 100 and 130 days were required to restore protein equilibrium, in which the nitrogen excretion equalled the intake. Similarly a patient with chronic duodeno-jejuno-ileitis with severe wasting before hospitalization was studied at intervals for five months after the relief of symptoms. Throughout this period she consumed between 20 and 25 gm. of nitrogen and about 2500 calories daily and remained essentially asymptomatic. Frequent balance studies (including the last) during this period showed consistent positive nitrogen balance, averaging 12 gm. of nitrogen daily. (Detailed studies of this patient are to be reported in another paper.) In these three patients there was no gain in weight during the last two months of this prolonged nitrogen storage—a fact difficult to explain. These observations, if generally confirmed, suggest that many of these patients never entirely repair their protein deficits when given diets containing moderate amounts of protein, ordinarily considered adequate. This state of chronic deficit may be a very important factor in predisposing them to recurrence of colitis set off by intercurrent infections, dietary upsets, emotional turmoil, etc.

Summary

The over-all protein metabolism of five patients suffering from chronic ulcerative colitis has been studied. All were found to have protein deficiencies as determined by nitrogen balance study on admission to the hospital. Three of the patients presented no signs of undernutrition on physical examination.

Positive nitrogen balance could be achieved and maintained in these patients by giving diets moderately high in protein with or without the parenteral administration of protein hydrolysates or blood. Although difficult to prove by observation under clinical conditions, it was our opinion that parenterally administered protein hydrolysate was relatively well utilized by these patients. The hydrolysate was probably not as beneficial as an equivalent amount of protein given orally, but was advantageous when used to supplement a high oral intake of protein.

Large fecal losses of nitrogen were not common and when present seemed to be due to purulent or bloody exudate rather than unabsorbed food (even when the dietary intake was high).

No patient improved clinically unless positive nitrogen balance had been achieved and maintained. In four instances positive nitrogen balance preceded clinical signs of improvement by several weeks. Follow-up studies on two of these patients and another to be reported elsewhere indicated that high protein feeding for several months may be necessary to correct the protein deficit in these patients.

It is not claimed that chronic idiopathic ulcerative colitis is primarily a manifestation of protein deficiency and no attempt has been made to compare the therapeutic efficiency of high protein administration with the other generally accepted forms of treatment (e.g., chemotherapy, psychotherapy, antibiotics, etc.). It is probable that all of these measures may be important in bringing about a remission. We wish to emphasize, however, the prevalence of protein deficiency in these patients and to point out that positive protein balance may be a necessary (though doubtless not sufficient) condition for clinical remission. We also would like to suggest that the period of time required for complete restoration of tissue protein may be quite lengthy and that a partially corrected unrecognized chronic protein deficiency may be a very important factor in permitting relapse of the disease.

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THE SHOULDER-HAND SYNDROME: A COMPLICATION OF CORONARY ARTERY DISEASE*

By A. W. Hilker, M.D., *Eau Claire, Wisconsin*

The condition of reflex dystrophy of an extremity following an injury has been discussed fully by many authors in the past 70 years. As early as 1877, and later in 1883, Wolff [1, 2] discussed trophic changes in the limbs following resection of a joint or following infection. In 1895 Kümmell [3] reported six cases of bone atrophy following injury. In 1900 Sudeck [4, 5] described fully the post-traumatic osteoporosis which is known as Sudeck's atrophy; in 1902 he wrote further on this subject and since that time there has been much in the literature with general agreement that this condition is a reflex dystrophy.

Recently de Takats [6, 7, 8] has written extensively on causalgia, post-traumatic, and its relation to Sudeck's atrophy and reflex dystrophy and he further describes its mechanism. In more recent years Sudeck's atrophy, causalgia or reflex dystrophy of an extremity involving a shoulder and hand has been noted as resulting from other causes than trauma. In 1948, Steinbrocker, Spitzer, and Friedman [9] published a most comprehensive study of the multiple conditions that produce a reflex dystrophy of an upper extremity; all, however, simulating the post-traumatic syndrome. The later authors' report was based on 42 cases of reflex dystrophy of the upper extremity developing from the following conditions: After myocardial infarction, post-traumatic, post-hemiplegic, post-herpetic and with cervical osteoarthritis. There were four cases with multiple or inconclusive etiology and 11 cases in which no apparent cause was found, and which were listed as idiopathic. Of the 42 cases reported, nine were a sequel to myocardial infarction. This great variety of causes originating far apart from each other, and apparently involving the involuntary nervous system without definite segmental distribution, has given rise to the recent and most acceptable neurophysiological explanation, namely, involvement of the internuncial pool in the spinal cord. Lorente de Nó [10] advanced this theory in 1938 in his article, "Analysis of the Activity of the Chain of Internuncial Neurons." In 1943 Livingston [11] elaborated on this concept as a neurophysiologic interpretation of causalgia.

Steinbrocker et al.[9] summarized this mechanism in the following statement, "Recent physiologic investigation shows this internuncial pool to be an extensive network of interconnecting neurons in the central gray matter, extending over many segments. At these levels potential connecting pathways are formed between incoming impulses and motor neurones of either the sympathetic (posterolateral) or anterior horn cells." This concept is gen-

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From the Department of Internal Medicine, Midelfart Clinic, Eau Claire, Wisconsin.

erally accepted as the most plausible explanation of the shoulder-hand syndrome from its variety of causes.

The purposes of this paper are to elaborate further the development of that form of the shoulder-hand syndrome associated with coronary artery disease and myocardial infarction, and to present possible additional contributing factors in the development of the syndrome from these conditions alone. The syndrome, following myocardial infarction or coronary artery disease, has been described in the literature, but reports have been few in number. This paucity of literature is really remarkable when one considers the frequency of its occurrence and the incapacity it produces. There is no doubt that such a syndrome exists following myocardial infarction. That can be stated with certainty, but what the pathological physiology is that promotes the condition is difficult to evaluate.

In 1930 Howard [12] discussed the painful shoulder with cardiac disease and attributed it to periarthritis. In 1936 Edeiken and Wolferth [13] wrote specifically about the persistent pain in the shoulder region following a myocardial infarct. Leech [14] in 1938 again discussed the painful shoulder in association with coronary artery disease. It was not until 1941 that Askey [15] presented 22 cases illustrating the hand and shoulder complication after a coronary occlusion. Meyer and Binswanger [16] in 1942 discussed three cases of periarthritis involving the joints of the hand and wrist following myocardial infarction. Kehl [17] in 1943 presented six cases of Dupuytren's contractures as a sequel to coronary artery disease and myocardial infarction and suggested irritation of the sympathetic ganglia as playing an important etiological rôle. Johnson [18] also in 1943 wrote that in 178 consecutive cases of myocardial infarction, 39 or 21.8 per cent developed disabling changes in the hand resembling sclerodactylia and he used the term "post-infarction sclerodactylia" to describe the syndrome. He suggested a sympathetic vascular reflex induced by cardiac pain producing anoxia and ischemia from vasoconstriction. In the 42 cases of reflex dystrophy reported by Steinbrocker et al.[9] nine were secondary to myocardial infarction.

In the past two years the author has collected 11 cases of this post-coronary syndrome. The frequency of its occurrence becomes more and more apparent. The incidence of this condition has previously been reported to be 10 per cent to 22 per cent of all the patients having myocardial infarction.[18] It is probable, however, that a great many cases of myocardial infarction in the first several weeks have some degree of ischemic changes of one or both hands. In some the condition is transient and completely reversible; in others minor but extremely annoying residuals remain. In approximately 20 to 25 per cent of the cases irreparable trophic changes of skin, tendons, muscle, fascia and bone lead to definite incapacity.

Symptoms

The onset of this complication occurs between three and 12 weeks following a myocardial infarction or after repeated serious bouts of angina pectoris.

The patients with angina pectoris, however, only develop the syndrome if there is evidence of myocardial insufficiency. It may occur with severe coronary artery disease without clinical evidence of an infarction, but it usually manifests itself more definitely following an occlusion. There is no predilection for involvement of any one side of the body; either the left or right upper extremity or both may become involved. Occasionally one shoulder and both hands, or both shoulders and one hand are affected. Not infrequently a first symptom is a painful shoulder and a sore, tender, swollen hand. The ultimate result is a contracted shoulder and marked trophic changes of the hand. At the onset the hand or hands become swollen, painful, tender and stiff, with various shades of discoloration ranging from red to blue. The hand or extremity is usually warmer than the other parts of the body. The skin of the fingers loses its normal wrinkles and movement is limited and painful. In some of the less severe cases physical findings may be few, yet the patient's symptoms regarding his hands may be great; not until a later date is it really apparent that a pathologic process existed.

In the first stage the hand is swollen, painful, tender, warm and discolored. A patient may recover completely at this point or he may go into a second stage. Here the swelling disappears but the pain and stiffness are persistent and progressive and movement becomes further limited. The hand usually becomes colder, the skin becomes thin and more attached to underlying structures. The muscles become atrophic and the hand loses its normal softness, the tendons are thickened and tender and the palmar fascia may be involved. A roentgen-ray of the hand shows marked trophic changes of the metacarpal and hand bones. If the shoulder is involved, there is a burning, painful joint, with limitation of motion and roentgen evidence of trophic changes of the end of the humerus. Even at this stage the pathology may be interrupted and partly reversible. Most persons who have gone on to this second stage, however, are crippled permanently to some degree. The process may continue and go into a third stage.

The end result or third stage is a contracted, claw hand with thickening and shortening of the tendon sheaths and palmar fascia, atrophy of the muscles and further trophic changes of the bone. The hand is cold, hard, stiff, contracted and immobile. The hand at this stage is very similar to that seen in reflex dystrophy following a severe injury to the arm, and the bone changes resemble those of Sudeck's atrophy.

Discussion of Cases

The series consisted of 11 cases of coronary artery disease, nine of them with myocardial infarction, in whom ischemic involvement of an arm and hand occurred, resulting in varying degrees of trophic changes. Some changes were minor and apparently reversible; others were marked, deforming, and permanently incapacitating.

Two patients had coronary insufficiency with angina pectoris but without

evidence of an acute myocardial infarction. In the first of these patients the data suggested coronary sclerosis but without electrocardiographic evidence of an acute infarct. This patient, however, was put to bed because of his progressive cardiac symptomatology. He was having more and more anginal pain with less and less exertion plus an increase in dyspnea. After approximately two and one-half weeks at bed rest the left shoulder and both hands became involved. Six months later the patient had a contracted left shoulder and bilateral painful trophic changes of the hands with approximately 30 per cent loss of function in flexion of the fingers and 50 per cent disability at the shoulder; he was able to elevate the arm only 90°. Although this patient had no electrocardiographic evidence of an occlusion nor myocardial infarction, and did not have an elevation of the sedimentation rate nor sustained substernal pain at rest, nevertheless, the fact that this syndrome followed may mean that actually an infarction was present. The subclavian, brachial, radial and ulnar pulses were easily palpable and seemed adequate.

This case might have been called arthritis, but the changes in the bone and hand were more characteristic of a Sudeck's atrophy and not characteristic of an arthritis. This patient never attained a good state of compensation, remains on the fence between myocardial insufficiency and compensation, being dyspneic with slight exertion and troubled with numerous extrasystoles and sometimes bigeminal rhythm.

The other patient, case 2, of coronary insufficiency and no evidence of an occlusion or myocardial infarction, was one with hypertensive heart disease with calcific aortic disease and marked aortic insufficiency plus angina of effort. Here, too, the symptomatology was progressive and the patient was put to bed. Four weeks later the patient developed a right shoulder and hand syndrome. Several weeks later the patient had a contracted right shoulder, being able to elevate the right arm only 35°, and trophic changes of the right hand with 50 per cent loss of function. This patient had severe hypertension and the aortic insufficiency with angina was of rather sudden onset. She became dyspneic at bed rest and had right basal crepitant râles. She did not respond very well to digitalization. After many weeks in bed the patient lost from 35 to 40 pounds in weight. The cardiac function improved and there has been steady improvement in the hand and shoulder function. Presently she is able to elevate her arm 65° and has 75 per cent function of the right hand.

Cases 3 and 4 have sustained the greatest loss of function, each with a cold, stiff, contracted, hard, immobile hand. Both had severe anterior myocardial infarcts and both had left massive pleural effusions. Their courses were almost identical except that one had involvement of the left shoulder and left hand, the other the right shoulder and right hand. The dystrophy in both started approximately one month after the infarcts and two weeks following the massive pleural effusion. They were in the hospital simultaneously, and each after seven weeks had a contracted shoulder and trophic hand, one the left and the other the right. Each patient had only 50 per cent

motion in the shoulder affected and 85 to 90 per cent loss of function in the hands. In both cases the peripheral circulation seemed adequate.

In case 3, the patient developed a massive pulmonary effusion secondary to multiple left pulmonary infarction following a coronary thrombosis. This patient had had prolonged hypotension and evidence of forward failure for several weeks and during this time the shoulder-hand syndrome progressed to the far advanced stage. Subsequently there was resolution of the chest condition and adequate myocardial function, but after several months there was little improvement in the trophic changes of the hand and shoulder. Case 4 developed a pulmonary complication following Dicumarol therapy for her myocardial infarction. Daily prothrombin times were taken prior to the administration of Dicumarol. Several days following the infarct the prothrombin was found to be 12 per cent; simultaneously the patient developed a pericardial friction rub that persisted for many days. During that week the left chest became dull to percussion and a roentgenogram revealed a massive effusion. It was suspected that she had a hemopericardium and that the effusion was also bloody secondary to the very low prothrombin. This patient also had prolonged hypotension and evidence of forward failure for several weeks and during this time the shoulder-hand syndrome began and progressed to an advanced stage. Subsequently there was resolution of the chest condition and an adequate myocardial function developed, but this patient, too, has had little improvement in the trophic changes of either the shoulder or the hand.

Cases 5 to 8 inclusive, with myocardial infarction, three anterior and one posterior, all developed hand pathology. Two of these also had shoulder involvement. Each had a painful, swollen, stiff hand that developed three to six weeks after the infarction and each had a varying degree of residual after one to one and one-half years. These residuals range from tender, thickened tendons to atrophy of muscle and up to 20 per cent loss of motion. Although this group shows least involvement the symptomatology here is nevertheless very disturbing.

One case, number 9, a man 44 years of age, had a severe anterior myocardial infarction. Five weeks after the infarction, he developed a swollen, painful left hand. This went through various changes until presently, eight months post-infarction, there is no residual, with complete return of function. There is no evidence of myocardial insufficiency.

Still another patient, case number 10, had coronary artery disease with angina and he developed a painful right shoulder with a mildly aching right hand but without appreciable physical changes. One year later, however, he developed a severe posterior myocardial infarction and three weeks after this there occurred a marked exacerbation of the right shoulder pain and definite swelling, discoloration and painful limited motion of the fingers of the right hand. Presently, six months later, the patient is suffering from a contracted right shoulder, being able to elevate his arm only 120° and also from a trophic hand with 25 per cent loss of finger flexion. The patient has little

myocardial reserve, being dyspneic on slight exertion and he has angina with minimal effort.

The last patient, case 11, two years ago had an anterior myocardial infarction. Three weeks after this occlusion, the patient complained of both shoulders aching and had painful swelling of the left hand. Four months later he was hospitalized for myocardial insufficiency. The left shoulder and hand at this time were further involved and he had marked diminution of function. His myocardium, however, again compensated well, but six months later he again went into decompensation. Presently he is in a state of chronic decompensation, dependent upon intramuscular mercuhydrin twice weekly, low sodium diet, fluid restriction and maintenance digitalis. The shoulder-hand syndrome became bilateral after the two bouts of decompensation with marked disability of both shoulders and hands. Both shoulders and both hands are presently involved with limitation of motion in each joint. All joints show marked trophic changes by roentgen-ray.

Discussion

The reason why this shoulder-hand syndrome develops following a coronary occlusion in one-fifth to one-quarter of patients cannot be given with certainty. The first week after a severe myocardial infarct, the patient uses his arms and hands very little; he is at absolute bed rest, he is turned and is fed by the nurse and naturally develops a certain degree of atrophy of disuse. Yet in most cases the shoulder and hand symptoms do not occur until three to five weeks after the infarct and by that time the patients are moving their extremities actively. The condition as it progresses is of a much more serious nature than one might expect from a simple atrophy of disuse. Most patients have had some degree of hypertension prior to the coronary occlusions, but at the time of the infarction and afterwards the blood pressure was comparatively low. Some patients have hypotension for a period of several weeks after the infarct. It is well known that a myocardial infarction of appreciable size causes decrease in cardiac output and some degree of forward failure.

Only patients with a myocardial infarct, who had signs of circulatory failure with prolonged hypotension, right basal pulmonary râles, and increased respiratory rate, developed the shoulder-hand syndrome, and no patient with angina pectoris developed the shoulder-hand syndrome unless there were signs of left heart failure. There appears to be a direct ratio between the severity of the myocardial infarction and the development of the shoulder-hand syndrome. There seems, in addition, to be an apparent direct ratio between the subsequent status of the myocardium and recovery from the shoulder-hand syndrome. A persistent myocardial insufficiency seems to aggravate and perpetuate the syndrome. A myocardium that promptly becomes competent after the onset of the shoulder-hand syndrome tends to interrupt this development and reverse the process toward a normal state.

If one accepts the most recent neurophysiological work regarding the etiology of this syndrome, then one might reason that with a myocardial infarction there is a disturbance of the electrical conduction of the myocardium which may set up a response in the sympathetic nerve plexus of the heart. This response is then carried through the inferior, middle and superior cardiac nerves to their respective cervical ganglions. The stimuli may then be transmitted to the spinal cord and into the internuncial pool. In the internuncial pool the stimuli may travel upward into the anterior horn cells, causing disability of the shoulder, or downward into the lateral horn cells or sympathetics innervating the whole upper extremity in the region of T_{-1} and T_{-4}. It may be reasoned that anoxia with defective local tissue nutrition might be the possible stimulus that perpetuates the condition, at least to far advanced changes. The correction of anoxia and of the defective local tissue nutrition would then be responsible for interrupting this cycle and reversing the process.

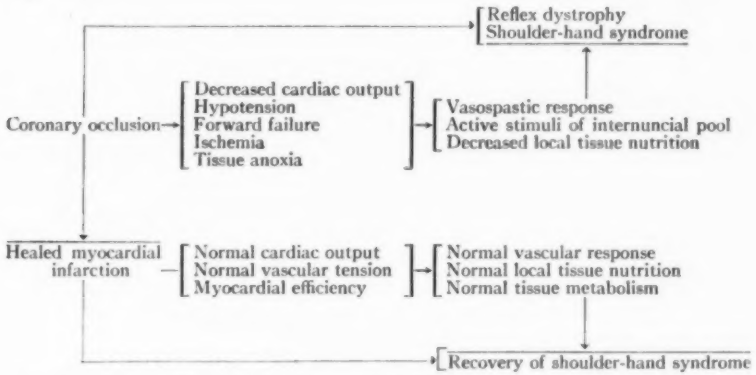

FIG. 1. Possible factors in the development of the shoulder-hand syndrome following myocardial infarction and the factors that may reverse the process.

The accompanying diagram (figure 1) illustrates the possible factors in the development of the shoulder-hand syndrome following myocardial infarction and the factors that may reverse this process. In any severe myocardial infarction there is decreased cardiac output, hypotension, evidence of forward failure with ischemia and tissue anoxia. These factors lead to a decreased local tissue nutrition and this decreased local tissue nutrition may be the active stimulus to the internuncial pool which sets up a vasospastic response leading to the reflex dystrophy of the shoulder-hand syndrome.

On the other hand, when the myocardium becomes healed and a normal cardiac output is restored, there is normal vascular tension. This then leads to normal tissue metabolism, normal local tissue nutrition, and therefore, one would expect a normal vascular response which in turn would lead to the recovery of the shoulder-hand syndrome. If, however, the pathologic process

in the spinal cord and internuncial pool is too far advanced due to the decreased local tissue nutrition, even good return of cardiac function may not alter the shoulder-hand syndrome. The damage already done is irreparable. Similarly, a persistent myocardial insufficiency will make the process irreversible. Reflex dystrophy due to injury is treated by a sympathetic block, but one hesitates in a patient with myocardial infarction to carry out such a procedure.

Summary

1. Eleven cases that developed a shoulder-hand syndrome as a result of severe coronary insufficiency or myocardial infarction are reported. The symptomatology is discussed and the condition described in its three stages.

2. Two of the 11 cases developed the shoulder-hand syndrome without evidence of acute myocardial infarction but both had angina with effort and evidence of left heart failure.

3. The nine remaining cases all had severe myocardial infarction. All patients had marked electrocardiographic changes, high sedimentation rates, prolonged hypotension, and evidence of forward failure for a week to several weeks following occlusion. In this series of cases no patient developed the shoulder-hand syndrome unless there was myocardial failure and prolonged hypotension. There is an apparent direct ratio between the severity of the myocardial infarction and the development of the shoulder-hand syndrome. It might be stated that the incidence increases in proportion to the size of the infarction.

4. Two of the nine cases developed the far advanced trophic changes described as the third stage. Both had severe anterior myocardial infarction and both had pulmonary complications, providing multiple causes for progression of the syndrome.

5. Those patients who regained good myocardial function tended to reverse the shoulder-hand syndrome toward normal, whereas persistent myocardial insufficiency tended to aggravate the shoulder-hand syndrome.

6. Recent neurophysiologic concepts are described as possible explanation of this syndrome and additional factors are suggested as possibly entering into the complex chain of events that are required for the development of the shoulder-hand syndrome.

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RECENT ADVANCES IN THE PATHOGENESIS AND TREATMENT OF ESSENTIAL HYPERTENSION*

By G. E. Wakerlin, Ph.D., M.D., F.A.C.P., *Chicago, Illinois*

By essential hypertension, of course, is meant chronic hypertension of unknown cause. Approximately 90 per cent of all hypertensions seen clinically belong to this group. The hypertensions of known causes include those associated with nephritis, pyelonephritis, renal anomalies, renal tumors, pheochromocytomas, adrenal cortical tumors, pituitary basophilism, coarctation of the aorta, and certain lesions of the central nervous system. The exact mechanism of the increase in arterial blood pressure in even this latter group, however, is definitely known only in the case of pheochromocytomas; viz., an increased secretion of epinephrine. Nevertheless, clinical differentiation of these hypertensions from essential hypertension is vitally important since there are definite prospects for cure by surgery in the case of hypertensions due to unilateral pyelonephritis, renal anomalies, renal tumors, and adrenal tumors. Finally, in defining and classifying hypertensions, note should be taken of the fact that hypertension, like fever and leukocytosis, is a sign of disease and not a disease itself. In other words, "essential hypertension" is a designation born of ignorance and is equivalent to "fever of unknown cause."

(a) *Hemodynamics.* In uncomplicated essential hypertension, the cardiac output is normal, the blood volume is normal, the viscosity of the blood is normal, and in early hypertension the elasticity of the arteries is more or less within normal limits for the particular age group of the patient. The factor responsible for the increased arterial blood pressure is the augmented peripheral resistance in the systemic vascular tree due to narrowing of the lumina of the arterioles. A greater head of pressure is necessary to force the blood through the narrowed arterioles into the capillary circulation. The relation between blood pressure and the caliber of the arterioles is such that if the arterioles become one-fifth narrower, the blood pressure doubles and the heart, of course, must meet the added load. In early essential hypertension, the arteriolar narrowing results from generalized arteriolar vasoconstriction, and not, as was formerly thought, predominantly from splanchnic vasoconstriction. As the hypertensive process continues, the augmented peripheral resistance becomes partially due to progressive arteriolosclerosis which is more pronounced in some areas of the body than in others, notably the kidneys, spleen, pancreas, liver, and brain, in decreasing order of intensity. Hypertension also appears to accelerate the progression of sclerotic changes in the larger arteries, including the coronaries.

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From the Department of Physiology, University of Illinois College of Medicine, Chicago, Illinois.

The work of the heart is increased in hypertension and roughly in proportion to the systolic pressure. As the hypertension continues, the left ventricle of the heart hypertrophies but the coronary blood supply tends to lag behind. Since the hypertensive heart functions at a higher than normal base, it possesses a distinctly reduced reserve. Moreover, the coronary arteries of hypertensives show a much higher incidence of arteriosclerosis than normotensives of similar age groups. These facts constitute the pathophysiologic bases for the cardiac complications of myocardial insufficiency and infarction.

The cerebral arteries have thin walls and are poorly supported by brain tissue since they lie in the perivascular spaces. Next to the coronary arteries and the aorta, the cerebral vessels are most subject to arteriosclerosis. The arterial branches supplying the region of the internal capsule are especially thin-walled and in direct line with the pressure wave from the heart. These facts form the pathophysiologic bases for the frequency of cerebral hemorrhage in hypertension.

With the passage of years progressive renal arteriolosclerosis causes a gradual decrease in renal function, although in the great majority of essential hypertensives renal function is still comparatively satisfactory when the hypertension is terminated by death from cardiac insufficiency or infarction, apoplexy, intercurrent disease, or old age. However, approximately 10 per cent of essential hypertensives succumb to renal failure. So-called malignant hypertension may be present from the start, or benign hypertension may suddenly change into the malignant form. The difference between benign and malignant hypertension is probably primarily quantitative with reference to severity and time. On the other hand, the typical lesion of benign hypertension is arteriosclerosis and arteriolosclerosis, whereas that of malignant hypertension is arterionecrosis and arteriolonecrosis. The renal vessels, as well as those of other tissues and organs are involved in the necrotizing process. As a consequence renal blood flow and renal functions are markedly reduced with resulting uremia and death.

(b) *Pathogenesis.* Recent studies have confirmed the facts that essential hypertension appears more frequently in certain families and in stocky, pyknic, overweight individuals. However, heredity and body type must operate through pathophysiologic mechanisms. In spite of recent extensive and productive laboratory and clinical research, the pathogenesis of essential hypertension is still obscure. This is true even though there are occasional categorical statements in the literature to the effect that essential hypertension is due to an increased secretion of the pressor enzyme, renin, by the kidney.

From the standpoint of pathogenesis, essential hypertension is probably a generic classification. The hypertensions due to pheochromocytomas, adrenal cortical tumors, and renal abnormalities were once classified under essential hypertension. As our knowledge increases, other species of hypertension will undoubtedly be split off. Current research on pathogenesis

points to neurogenic, renal, and endocrine factors, each of which may ultimately delineate a future, separate species of hypertension.

A certain portion of essential hypertensives show a significant reduction in blood pressure when subjected to sedation or to general anesthesia. This is also true for spinal anesthesia which blocks the preganglionic vasoconstrictor fibers, or tetraethylammonium chloride which blocks autonomic ganglia, and dibenamine which paralyzes vasoconstrictor nerve endings in the arteriolar wall. Likewise some patients show lasting reductions in blood pressure from sympathectomy. These findings suggest but do not prove that a group of essential hypertensives have their increased blood pressure primarily on the basis of augmented vasoconstrictor nerve activity. This may in turn be due to increased tonus of the medullary vasomotor center consequent upon corticohypothalamic imbalance (nervous tension). Some psychiatrists consider the typical hypertensive personality as alternating between aggression and passiveness and thereby subject to strong emotional conflict. Neurogenic hypertension has been produced in the dog by section of the aortic depressor and carotid sinus (buffer) nerves, with resulting release and increased tonus of the vasoconstrictor mechanism. Although this form of experimental hypertension differs in several respects from essential hypertension (viz., increased cardiac output, increased heart rate, and absent buffer nerve function) further study of experimental buffer nerve hypertension may well shed light on the pathogenesis and pathophysiology of essential hypertension. In any event, many patients with essential hypertension show a neurogenic component, even though their hypertensions may ultimately prove to be on other pathogenetic bases.

The classic method of Goldblatt; viz., partial constriction of the renal arteries, produces a hypertension which in many respects resembles essential hypertension. Accordingly, attention has been focused on the possibility of pathogenetic involvement of the kidney in essential hypertension. Unfortunately the mechanism whereby constriction of the renal arteries produces hypertension in the experimental animal has not yet been determined. It is assumed but not completely proved that moderate renal ischemia is necessary to set off the pressor mechanism, which has been suggested to be an increased secretion of renin, a decreased secretion of a depressor substance, or an increased formation of pressor amines by the kidney. None of these three hypotheses has been proved, although there is suggestive evidence for each. Hence, it is not surprising that there is no definite proof for an increased secretion of renin in essential hypertension. Indeed, the recent employment of a highly sensitive method for the assay of renin shows no difference in the renin content of the systemic blood of essential hypertensive and normotensive humans. Of course, the essential hypertensive may be more sensitive to renin but this has not been proved to date. There is likewise no good evidence for the renal depressor or amine hypotheses as operative in essential hypertension. Although many patients with essential hypertension show renal ischemia, some patients with early essential hypertension

appear to have normal renal blood flows, so that the significance of renal ischemia in the pathogenesis of essential hypertension, as in experimental renal hypertension, is still unsettled.

There is some evidence suggesting that injections of the corticotropic hormone of the anterior pituitary may produce experimental hypertension in rats, presumably through stimulating increased secretion of adrenal cortical hormones, one or more of which may be directly vasoconstrictor or may possibly in turn increase the output of renin from the kidney. The maintenance of experimental renal hypertension is dependent upon adequate anterior pituitary and adrenal cortical functions. On the clinical side, a minority of patients with essential hypertension show an increased tolerance to insulin, large doses of desoxycorticosterone have produced hypertension in normotensive humans, sodium chloride metabolism is mildly altered in essential hypertension, and marked sodium chloride restriction has an antihypertensive effect in some essential hypertensives. These findings suggest but do not prove that a certain undetermined proportion of patients with essential hypertension may have increased adrenal cortex function as the pathogenetic basis for their elevated blood pressure. The cortex might differentially produce an augmented secretion of an as yet unknown cortical steroid with a predominant vasoconstrictor effect and with minimal effects on carbohydrate and salt metabolisms.

(c) *Treatment.* Recent advances in treatment have likewise not been decisive. There is still no "magic bullet" for the therapy of uncomplicated essential hypertension. Psychotherapy (by a psychiatrist, if necessary) is still an important adjunct. The benign character of essential hypertension in certain patients is sometimes forgotten. Any program of mental and physical rest outlined for an essential hypertensive should be individualized and guided by every-day, practical considerations. Intermittent courses of one of the barbiturates will remove some of the nervous tension. Certain new drugs which are capable of blocking vasoconstrictor nerve impulses are being tested in the treatment of essential hypertension. In this group are tetraethylammonium chloride, dibenamine, dihydroergotamine, dehydroergoclonine, and certain Veratrum derivatives. Tetraethylammonium chloride has already proved of value in the study of essential hypertensives to determine their suitability for sympathectomy.

Although certain renal extracts have proved of therapeutic value in experimental renal hypertension, no one has yet prepared a consistently potent, sufficiently purified renal extract suitable for trial in human hypertension. Certain marine and fish liver oils and fractions thereof have been studied therapeutically in experimental renal hypertension and have been shown inconstantly to contain variable amounts of an orally effective antihypertensive agent which is not vitamin A. Years ago radical restriction of protein and salt was recommended by some authorities. Recently a low protein, low salt diet consisting principally of rice and fruit has been recommended on the thesis that the kidney is involved pathogenetically in essential hyperten-

sion and that the work of this organ is reduced by the low protein, low salt diet. Obviously the pathophysiological basis of this therapy is hypothetical. Nevertheless, significant reductions in blood pressure have occurred in some patients on the so-called rice diet. In keeping with the dictum that moderation in all things is the keynote for living with essential hypertension, excessive ingestion of food should be avoided and if the patient is overweight a moderate reducing diet should be prescribed. For the essential hypertensive of normal weight, however, a protracted adherence to the low calorie, low vegetable protein content of the rice diet must inevitably lead to undernutrition and indeed to malnutrition.

Recently there has been a revival of radical restriction of sodium chloride in the dietary (700 mg. or less per day). Possibly the 10 to 20 per cent of essential hypertensives who show significant reductions in blood pressure on low salt will ultimately be found pathogenetically to constitute a separate species of hypertension. The rice diet may act mainly through salt restriction.

In keeping with the possibility that some patients may have essential hypertension primarily on an endocrine dysfunction basis, therapeutic effects have been reported from the use of pituitary extracts. These effects have been ascribed to the development of antihormones with a resulting neutralization of an hypothesized increased secretion of anterior pituitary or posterior pituitary hormones. However, in this and many other therapeutic studies of essential hypertension, sufficiently prolonged control periods have not been used and the important effect of concomitant psychotherapy has not been adequately considered.

Of the many drugs, vitamins, and tissue extracts that have been used in the treatment of uncomplicated essential hypertension, only the sedatives, the vasodilating nitrites, nitrates, and xanthine derivatives, and potassium thiocyanate can be considered of possible benefit. Nitrites and nitrates and the xanthines, although vasodilator in sufficient dosage, have been shown by carefully controlled experiment to be without significant effect in ordinary clinical dosage on the blood pressure and symptoms of essential hypertension (except for accompanying psychotherapeutic response). Yet there are some who postulate that these vasodilators may delay the progress of arterio- and arteriolosclerosis, despite the absence of satisfactory supporting evidence. The nitrites, nitrates, and xanthines are of value, however, in the treatment of angina as a complication of essential hypertension. The status of thiocyanate therapy is still controversial. Proponents admit that to obtain a significant reduction in blood pressure, a certain blood thiocyanate level must be maintained and that this is not far from the toxic level. Moreover, occasionally a toxic effect is produced even at what is considered to be a safe level. Obviously, if blood thiocyanate determinations can not be made at intervals, the therapy should not be used. The preponderance of recent evidence casts doubt on the efficacy of this drug in essential hypertension.

Thiocyanate may have a slight sedative action or may act merely through a nonspecific, toxicological depressor effect.

The estrogens and androgens have no specific effect against essential hypertension, although they will relieve climacteric symptoms which may aggravate a concomitant hypertension. Vitamin A, members of the B complex, and vitamins C, E and K have all been found to be without value in the treatment of essential hypertension. The same may be said for histamine, mecholyl, pancreatic extracts, garlic and parsley, liver extracts, and other preparations, even though some of these are still advertised and sold.

Sympathectomy has no lasting effect on the blood pressure of normotensive or renal hypertensive dogs, although the blood pressure of neurogenic hypertensive animals is lowered. This does not preclude the possibility that this procedure may be of value in essential hypertension since the similarities between experimental renal hypertension and essential hypertension do not necessarily mean even a partial common pathogenesis. Although sympathectomy has no lasting effect on the blood pressure of normotensive humans, there might conceivably be a difference between normotension and essential hypertension in this respect. A critical examination of the results reported for partial and complete sympathectomy, however, leads to less optimistic conclusions than some of the authors draw. Some authorities even question whether there is a significant effect from sympathectomy in essential hypertension and ascribe any improvement to psychotherapy, altered living regimen, and the nonspecific effect of the operative procedure. However, a minority of essential hypertensives, variously estimated at 10 to 20 per cent, do obtain what appears tantamount to a cure. Unfortunately, the methods of preoperative study presently available are not too satisfactory in differentiating patients who will obtain an excellent result from sympathectomy. This group may ultimately be segregated from the genus, essential hypertension, as having an elevated pressure primarily on a neurogenic basis. Whether the long range outlook for the majority of essential hypertensives subjected to sympathectomy is materially altered by the procedure is presently unanswered. Sympathectomy will, of course, definitely reduce the pressor component of emotional states and other forms of stress.

Summary

Essential hypertension is fundamentally due to slight generalized arteriolar vasoconstriction of the systemic circulation, with compensatory increased force of cardiac contraction. The fundamental pathogenesis of this vasoconstriction is not yet established. Increased tone of the vasomotor system, a renal pressor effect, or an altered anterior pituitary-adrenal cortex relationship may be involved. Within the genus, essential hypertension, there may be three or more species of hypertension corresponding to these mechanisms and others presently unknown. Cortico-hypothalamic imbalance may exert an effect through any of these three mechanisms and unquestionably this

factor, through increased vasomotor tone, plays an aggravating rôle even though the elevated blood pressure of essential hypertension may be primarily on a renal, endocrine, or other basis.

Obviously the treatment of essential hypertension is still relatively unsatisfactory. Medical management includes psychotherapy, judicious reordering of the patient's living, and the intermittent use of sedatives, particularly when the first two measures do not relieve nervous tension. The nitrites, nitrates, and xanthine derivatives may be used, although their value is questioned. Sodium thiocyanate is on the wane, although with due allowance for its shortcomings, the drug may have some value. The possible antihypertensive effects of protein and of sodium chloride restrictions are being redetermined. Certain sympathetic blocking drugs are under study. Antihypertensive renal and marine oil principles are still in the animal stage of investigation. Of the many other medicinal agents recommended for essential hypertension, none has been shown to be of definite value. Sympathectomy may be curative in a minority of essential hypertensives and of possible value in others. Further and more critical studies of the surgical treatment of essential hypertension are necessary.

Conclusions

The solution of the enigma of essential hypertension is dependent upon further work in the laboratory and clinic, looking toward determination of causes, pathogenesis, and more exact pathophysiology. Once these are known, treatment will become rational, specific, and more effective.

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CASE REPORTS

POLYCYSTIC DISEASE OF THE LIVER; REPORT OF TWO CASES DIAGNOSED BY PERITONEOSCOPY*

By David Niemetz, M.D., Archer Sokol, M.D., and Lester Meister, M.D.,
Beverly Hills, California

A review of the available literature [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11] of the past 10 years with reference to this uncommon anomaly, in its isolated form or in association with cystic disease of other organs, indicates that its diagnosis in the reported cases has been established at autopsy or by recourse to laparotomy. This report is presented to illustrate the diagnosis by means of peritoneoscopy.

Case Reports

Case 1. A Mexican female, 68 years of age, entered the Los Angeles County General Hospital July 25, 1946, complaining of loss of appetite, increasing fatigue, and weight loss of 10 pounds during the preceding four weeks. She had been referred to the hospital by a physician because of the foregoing complaints. Associated were symptoms suggestive of active pulmonary tuberculosis, consisting of occasional night-sweats and expectoration of blood-streaked sputum. She also complained of vague, right upper abdominal distress, occurring after eating fatty foods. Her lack of appetite was attributed to heartburn. On physical examination, her temperature was 99.4° F. (37.4° C.), pulse 80, and respirations numbered 20. The blood pressure was 150 mm. Hg systolic and 80 mm. diastolic. Examination of the chest showed a slight degree of supraclavicular wasting bilaterally. Harsh bronchovesicular breath sounds and fine râles were heard at both apical areas. The liver edge was palpated 9 cm. below the right costal margin at the midclavicular line. It was fairly sharp, non-tender, and extended across the abdomen to the opposite costal margin. The surface and the edge exhibited irregular nodularity. The lower pole of the left kidney was readily palpable, but was not fixed or otherwise remarkable. A small, reducible, soft, non-tender mass was discovered in the right inguinal area. The remainder of the physical examination was normal. Laboratory studies were as follows: Hemoglobin 58 per cent (9.9 gm.), erythrocytes 2.9 million, leukocytes 7,500, with a normal differential count. Urine (catheterized specimen) showed: specific gravity 1.012; pH 5.0; sugar 0, albumin 0; microscopic: 10 leukocytes per high power field, without erythrocytes or casts. Stool specimens (two) were negative for occult blood. Kahn reaction was negative, and the Wassermann reaction was positive on two occasions. (Roentgenographic examinations showed metallic deposits in the buttocks.) A barium enema showed no abnormality of the colon. However, the liver was noted to have an unusually broadened, rounded lower margin. Barium examination of the upper gastrointestinal tract revealed the stomach to be displaced ventrally. A postero-anterior film of the chest showed evidence of bilateral apical fibrotic and exudative tuberculosis. Three 24-hour sputum concentrates were negative for acid-fast organisms.

* Received for publication June 10, 1947. From the Departments of Medicine, University of Southern California and College of Medical Evangelists, at the Los Angeles County General Hospital.

At this point, peritoneoscopy was considered the procedure of choice. This was performed by one of us (D. N.) with the following findings:

"The parietal and visceral peritoneal surfaces were clear and glistening. There was no evidence of free fluid. The liver appeared to be obscured and its substance considerably replaced by masses of grape-like cysts, 0.5 centimeter to 3.0 centimeters in diameter. These appeared to arise from the liver substance and also from each other. The larger cysts transmitted light readily. The smaller were firm and were biopsied with some difficulty. Several small brownish areas suggestive of relatively normal liver tissue were noted. The entire liver was moderately enlarged. Due to adhesions, the pelvic organs were not visualized. The rest of the abdomen revealed no abnormality.

Impression: (1) Metastatic or primary carcinoma of liver; (2) polycystic disease of liver."

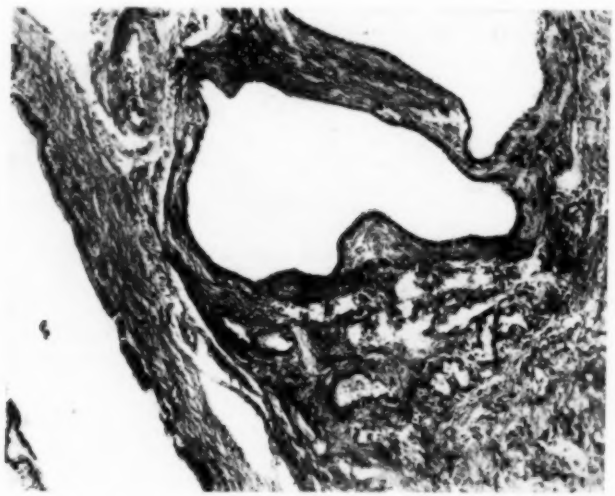

FIG. 1. Cystic areas in liver. Hematoxylin and eosin. × 250.

The biopsy (figures 1 and 2) report was as follows: "Grossly, the specimen consists of a small biopsy of the liver measuring 4 by 3 by 3 millimeters. On microscopic examination, sections reveal a stroma of dense fibrous tissue in which three or four larger cysts and several tiny cysts are present. The cysts are lined by cuboidal to low columnar epithelium, basophilic in staining, resembling bile-duct epithelium. A small group of liver cells is seen in one part of the section. The diagnosis is polycystic disease, liver."

Following the above report, further laboratory study was done, chiefly to determine the functional status of the liver and the existence of cystic disease of other organs. The serum bilirubin level was 0.2 milligram per 100 cubic centimeters. Urinary urobilinogen was negative in 1:10 dilution. The serum albumin was 4.4 grams and the serum globulin 2.6 grams per 100 cubic centimeters. Prothrombin activity of the plasma was 65 per cent of normal. Cephalin-cholesterol flocculation was 1+ at 24 hours and 3+ at 48 hours. Thymol turbidity of 3 units was within

normal limits. The bromsulfalein excretion test (dose of 5 milligrams/kilogram) showed 29 per cent of dye retained after 45 minutes. Serum alkaline phosphatase was 6.6 Bodansky units. An oral glucose tolerance test with 100 grams of glucose showed the following blood sugar values in milligrams per 100 cubic centimeters Folin-Wu: Fasting, 99; 15 minutes, 108; 30 minutes, 129; 45 minutes, 146; 60 minutes, 180; 120 minutes, 210. Urine diastase excretion was less than 1,000 units (normal). The non-protein nitrogen of the blood was 35 milligrams per 100 cubic centimeters. Serum inorganic phosphorus was 3.8 milligrams per 100 cubic centimeters. A modified Mosenthal test showed a normal range of specific gravity. The fractional phenolsulfonephthalein excretion was also normal. Excretory and retrograde urography were done, revealing no radiologic evidence of renal polycystic disease. The right kidney appeared to be displaced downward by the enlarged liver, and the left kidney was also low in position. Both renal pelves were moderately rotated.

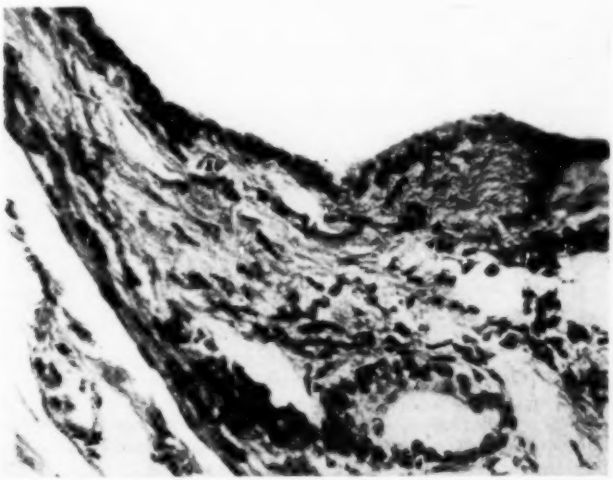

FIG. 2. Cystic areas in liver. Hematoxylin and eosin. × 500.

The patient's presenting symptoms disappeared within a few days following entry in July. On September 17, 1946 an incarceration of the right indirect inguinal hernia occurred. This was relieved by appropriate surgical means, with a normal convalescence. The hemogram became normal prior to the patient's discharge from the hospital, at which time she was referred to the chest and gastroenterology clinics.

Case 2. E. B., a 48 year old Negress, was admitted November 20, 1947 with complaints of abdominal tenderness and intermittent pain throughout the abdomen for nine years. During this time she never had felt well. Occasional tarry stools were noted during the past year. Anorexia, nausea, and vomiting were present for two days prior to entry.

Past history included the usual childhood diseases, typhoid fever, and fever diagnosed without blood smears as "malaria" when a child. At the age of 28 an unspecified type of abdominal tumor had been removed via a lower midline incision. A chronic conjunctivitis and rare, transient yellowing of the sclerae had been present for nine years. One year before admission evanescent swelling of feet and ankles

occurred, lasted two or three weeks, and did not recur. Menses were regular until one month prior to entry when the flow persisted for the 30 days preceding admission. She was a moderate user of alcohol but had not curtailed dietary intake.

Physical examination revealed an asthenic, fairly well nourished, apprehensive Negro female, with swollen abdomen, in no acute distress. Blood pressure was 190 mm. Hg systolic and 110 mm. diastolic. Conjunctivae were injected. Sclerae were not icteric. Pupils were round, equal, and reacted promptly to light and accommodation. The thyroid, cervical lymph nodes, breasts, and axillary nodes were normal. The lungs were clear and resonant. The heart was not enlarged, its rhythm was regular, and there were no murmurs. The abdomen was slightly distended. A well-healed narrow suprapubic scar was present. The hard, tender liver edge and surface were studded with 1 to 3 cm. nodules. The lower edge extended to the right iliac crest, and was attached to a mass in the left upper quadrant which extended 6 cm. below the costal margin. Spleen, kidneys, and other masses were not palpated. Pelvic examination revealed hard Skene's glands, cervix in midposition, corpus enlarged twice normal size, adnexae clear.

During her stay in the hospital she had almost constant dull, right abdominal pains with intermittent sharp, severe right upper quadrant pains and transient increases of distention.

Laboratory Procedures. Blood (entry): Hemoglobin 12 gm.; white blood cells 4,700; polymorphonuclears 53 per cent, lymphocytes 47 per cent. Urine (entry): Albumin and sugar negative; microscopic: no abnormal formed elements. Feces were repeatedly negative for occult blood. No parasites nor ova were seen. Kahn reaction (entry) was negative.

Roentgen-rays: Fluoroscopy of abdomen after barium ingestion (November 21, 1947): Stomach displaced to the left by large, palpable mass in right upper quadrant, extending anteriorly to, below, and far to right of stomach. Barium enema (December 30, 1947): No intrinsic colonic lesion. Mass in right upper quadrant presses transverse and descending colon to left. Chest (January 5, 1948): Lungs, heart, and aorta normal.

Icterus index: 7 (December 4); 5 (December 12). A/G ratio: 4.4/3.1 (December 4); 4.4/3.3 (December 12). Thymol turbidity: 3 units on December 4 and 12. Cephalin-cholesterol flocculation: Negative on December 4 and 12. Prothrombin time: 65 per cent of normal (December 12); 65 per cent of normal (December 20). Liver aspiration biopsy (December 22): chronic inflammatory tissue with a few liver cords. Insufficient material to make a definite diagnosis. Liver aspiration (Dr. William Mollé, January 14, 1948): 50 c.c. thin, chocolate-brown fluid. Smear: Few polymorphonuclears. Culture: No organisms grown. (January 20, 1948): 15 c.c. fluid material, apparently loculated. Culture: negative. (January 23, 1948): 80 c.c. Culture: negative. (January 26, 1948): 50 c.c. Culture: negative.

Therapy: On the basis of a past history of diarrhea ("typhoid"), and the recovery of chocolate-brown fluid from hepatic aspiration, a tentative diagnosis of amebic liver abscess was entertained and three courses of emetine were given on January 14, January 26, and February 4, 1948. Carbarsone was given in conjunction with the second course. No clinical improvement was apparent.

Sigmoidoscopy (February 13, 1948): Internal and external hemorrhoids. Slight bleeding, mucosa hyperemic to four-inch level, but no ulcerations or abscesses apparent.

Peritoneoscopy (February 26, 1948, Dr. Robert Hope). Pre-peritoneoscopic diagnosis: Polycystic liver disease. Post-peritoneoscopic diagnosis: Same. The peritoneum was clear, shining, and free from metastases. No free fluid was apparent. The liver was immense, with right edge down to iliac crest, irregular, studded with varied-size thin, bluish cysts. In fact, very little liver tissue was seen except in lower right lobe, where it appeared quite injected, evidencing a moderate degree of hepatitis.

Here the cysts ranged from a few millimeters to larger, up to one centimeter in diameter. Diagnosis: Polycystic liver disease.

Course following peritoneoscopy: Severe ileus developed, and continual suction via Levine tube was applied. After seven days this was discontinued and soft diet commenced. The patient was released one week later, on March 13, 1948, with some right upper quadrant tenderness still present. She was referred to the Outpatient Department for further investigation as to the presence of cystic involvement of kidneys and pancreas, which was not evident, however, in her clinical findings in the hospital.

Comment

1. The finding of definite functional impairment of the liver is not surprising in case 1, since the degree of involvement of the liver parenchyma was extreme. The fact that liver function was not more disturbed can be attributed to the very slow progress of the condition.

2. Of 499 cases of cystic disease of the liver of all types reported by Davis,[1] 152 had cystic disease of the kidneys. Detailed studies in case 1 showed no evidence of this association, nor was evidence obtained establishing pancreatic involvement.

3. The microscopic findings present in case 1 are consistent with those described by Wooten [6] in congenital anomalies of this type.

4. In case 1 peritoneoscopy was instrumental in revealing a relatively benign process where malignant disease of the liver was suspected.

5. Case 2 confirms the impression that the appropriate diagnosis in this condition can be offered clinically and safely confirmed by peritoneoscopy. Liver aspiration biopsy appears to offer inadequate information and may be misleading if fluid is obtained resembling that seen in amebic abscess of the liver.

Summary

1. Two cases of polycystic disease of the liver, diagnosed by peritoneoscopy, are presented, with illustrations of the microscopic pathology in one.

2. Impaired liver function was demonstrated in these cases.

3. Evidence of cystic disease of the other organs was sought with negative results.

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KAPOSI'S SARCOMA WITH SECONDARY INVOLVEMENT OF THE JEJUNUM, PERFORATION AND PERITONITIS *

By Nathan Mitchell, M.D., and Isidore A. Feder, M.D., F.A.C.P.,
Brooklyn, N. Y.

Since Kaposi's original description of multiple hemorrhagic sarcoma of the skin in 1872, more than 600 cases have been reported in the literature. In the great majority of these cases the skin has been primarily affected. A large number progress slowly for many years and at autopsy show no spread beyond the cutaneous site. However, the finding of sarcomatous deposits in the viscera is a common one. Almost every organ of the body has been implicated. In addition to the skin the most frequent sites of involvement are the penis, the gastrointestinal tract, the upper and lower respiratory tracts and the superficial and deep lymph nodes.[1] Unusual localizations include the serous membranes, spleen, liver, adrenal glands, myocardium, mesentery, diaphragm, urinary bladder, thyroid and brain.[2] Because of such widespread systemic involvement this disease must be kept in mind in the differential diagnosis of conditions manifesting multiple systemic complaints and physical findings. The alimentary canal may be involved wholly or in part from the oral cavity to the anus. The stomach and small intestine are most often affected, the large intestine and appendix less frequently. Gastrointestinal symptoms are not as a rule prominent but instances of severe diarrhea, abdominal pain, and hemorrhage have been described.[3] A recent case is recorded [4] in which a 17 year old boy died of intestinal intussusception caused by a solitary Kaposi nodule in the ileum. It has been emphasized that "death may occur from infiltration of the lungs, liver or spleen but by far the most common sequence is metastasis to the intestinal mucosa with ulceration causing hemorrhage and exsanguination." [5] The statement has been made that "intestinal perforation and intraabdominal adhesions have not been described."[1]

It is the purpose of this presentation to record a case of Kaposi's sarcoma in which the skin was involved for many years before a secondary mass in the jejunum perforated, causing generalized peritonitis and death.

Case Report

A Russian Jewish male, aged 69, was admitted to the Beth El Hospital September 13, 1946 with a chief complaint of pain in the left upper abdomen. The present acute

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From the Departments of Pathology and Medicine of the Beth El Hospital.

illness had started six days previously when the patient was seized with a severe attack of upper abdominal pain and profuse vomiting, first of ingested food and then of a bile-stained mucoid material which contained streaks of blood. On the following day the temperature rose to 102° F. There was a tarry stool, and the pain became localized in the left upper quadrant. Under conservative management the intensity of the pain diminished, the temperature receded, and the vomiting ceased. The patient was admitted for observation and study.

The past history disclosed the following. Fourteen years preceding admission the patient noticed the appearance of nodular swellings on his forearms and hands and had difficulty in flexing his fingers. Biopsy disclosed Kaposi sarcoma. Under roentgen-ray treatment these swellings disappeared. They recurred four months later. There was no pain nor other sensory disturbance. Crops of these lesions recurred periodically on the upper extremities. These responded at all times to radiation therapy. In 1940 some of the lesions on the right forearm became ulcerated. At about this time lesions were observed on the feet and subsequently on the legs. Some of these also broke down. The ulcerated lesions discharged a purulent material and then healed, leaving dry, brown scaly areas. In 1943 ulcerations on the right forearm appeared which failed to heal and extended despite therapy. An amputation of the right arm at the mid-humerus was performed at Memorial Hospital. The amputated member was described as "a seething mass of multinodular ulcerating and necrotic Kaposi's disease. Tumor nodules varied from a few mm. to 2 cm. in diameter. The larger masses were necrotic and foul-smelling. The entire extremity was edematous. There was no tumor in the lymph nodes accompanying the specimen." Following the amputation only occasional, isolated nodules appeared in the skin. These were surgically excised, the most recent one on the left thigh about four weeks before admission.

About one year prior to the present illness the patient began to experience attacks of dull, generalized abdominal cramps and nausea. The cramps lasted only a few minutes, recurred frequently during the day and night and were neither related to nor relieved by food. The attacks increased in frequency and severity, and about two months before admission the patient began to vomit after meals. The vomitus was bile-stained and contained ingested food but no blood. He was placed on ulcer treatment without relief. There had been a weight loss of about 35 pounds in the past year.

Physical examination disclosed the following. The eyes, ears, nasal and oral cavities were negative. The neck showed no adenopathy. The heart and lungs were negative. The blood pressure was 110 mm. Hg systolic and 90 mm. diastolic. There were moderate tenderness, spasticity and an indefinite mass the size of an orange in the left upper quadrant. Rebound tenderness was present. The liver and spleen were not palpable. Rectal examination was negative. There was a well healed amputation stump at the level of the right mid-humerus. A number of enlarged firm lymph nodes were present in the right axilla, the largest being the size of a walnut. Throughout the skin, but most marked on the extremities, were numerous flat pigmented areas. The skin over the legs and feet was dry and scaly.

The temperature was normal, the pulse rate slightly increased. The blood count showed a hemoglobin of 54 per cent, and 2,960,000 red blood cells. Differential smear showed 84 per cent polymorphonuclear cells, 6 staff cells and 10 lymphocytes. The sedimentation rate was 17 minutes for 18 mm. The urine showed a faint trace of albumin and an occasional red blood cell. Occult blood was present in the stool.

Course. The patient continued to improve during the first three hospital days. The temperature remained normal. The pain completely subsided. The abdomen became soft, the suggestive mass disappeared, and the tenderness in the left upper quadrant was minimal. On the fourth day, while straining during defecation, the

patient was seized with excruciating, generalized abdominal pain and vomited a large amount of food and blood. Examination disclosed a boardlike rigidity of the abdomen with marked generalized direct and rebound tenderness. The patient's condition rapidly deteriorated. The temperature rose to 105° F., and he died 12 hours later. Perforation of a Kaposi sarcoma, primary neoplasm, peptic ulcer or diverticulitis somewhere along the gastrointestinal tract, were all considered in the differential diagnosis.

The history of attacks of abdominal cramps and vomiting, with weight loss, suggested the presence of a gastrointestinal malignancy. The onset of the present illness with pain and evidence of peritoneal irritation pointed to a perforation of the neoplasm. Kaposi sarcoma of the skin had been previously diagnosed. The right axillary glands were apparently involved in the same process. Because visceral manifestations, especially in the gastrointestinal tract, are not infrequent in this disease it was postulated that the intestinal lesion was similar to that present in the skin and nodes. Death was apparently due to generalized peritonitis resulting from a reperforation of the neoplasm occasioned by the straining at stool.

FIG. 1. A probe inserted into the ulcerated jejunal mass is shown projecting through the perforation near the mesenteric border.

Autopsy Findings. The pertinent findings were limited to the abdomen and to the right axilla. The peritoneal cavity contained one and a half liters of purulent fluid. The visceral peritoneal surfaces of contiguous small bowel were covered by recent fibrinous exudate.

A large firm mass 8 by 3 by 3 cm. (figure 1) completely encircled the proximal jejunum at a point 6 feet from the ligament of Treitz. Over the right anterolateral aspect of the jejunal wall a perforation 0.8 cm. in diameter was present which led into the bowel lumen. The edges of the perforation were covered by organizing fibrin. Sections of the jejunal wall revealed a centrally ulcerated grayish tumor

FIG. 2. A sagittal section through the jejunum reveals the hemorrhagic mass infiltrating its wall.

mass which was well demarcated from the surrounding intestinal wall (figure 2). No other foci of tumor tissue were present in the gastrointestinal tract.

The large right axillary mass was composed of discrete lymph nodes, the largest measuring 4 cm. in diameter (figure 3). The architecture of the nodes was replaced by soft gray opaque tumor tissue marked by focal hemorrhage and necrosis. No active skin lesion either grossly or microscopically, was found. Small accumulations of hemosiderin laden phagocytes were noted in a dermis that was densely fibrotic. Careful examination of the other viscera revealed no metastatic foci.

Microscopic Description. Sections from the base of the jejunal ulcer revealed a malignant spindle cell tumor showing definite vasoformative tendencies (figure 4). The individual tumor cells were spindle shaped with oval to rounded vesicular nuclei. Hyperchromatism and cellular pleomorphism were evident. A moderate number of mitotic figures was seen. The tumor tissue extended through the entire thickness of the jejunal wall, and the edges of the grossly described fistula were lined by neoplastic tissue which was partially necrotic and acutely and chronically inflamed. The

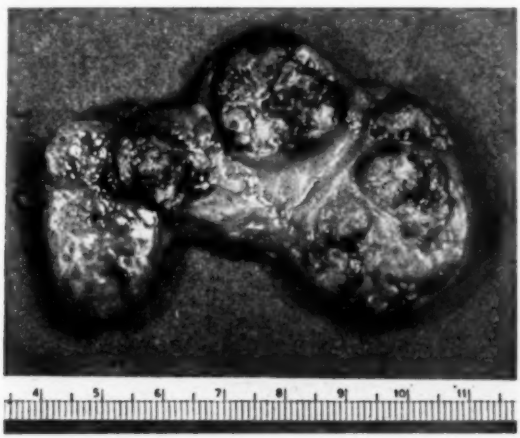

FIG. 3. The enlarged right axillary nodes show focal necrosis and hemorrhage in the metastatic tumor tissue.

axillary lymph nodes were completely replaced by neoplastic tissue which was focally necrotic and hemorrhagic. The individual tumor cells were spindle shaped with cytologic characteristics quite similar to those seen in the jejunal mass. The tendency to form vascular channels was much less distinctly shown in the involved lymph nodes.

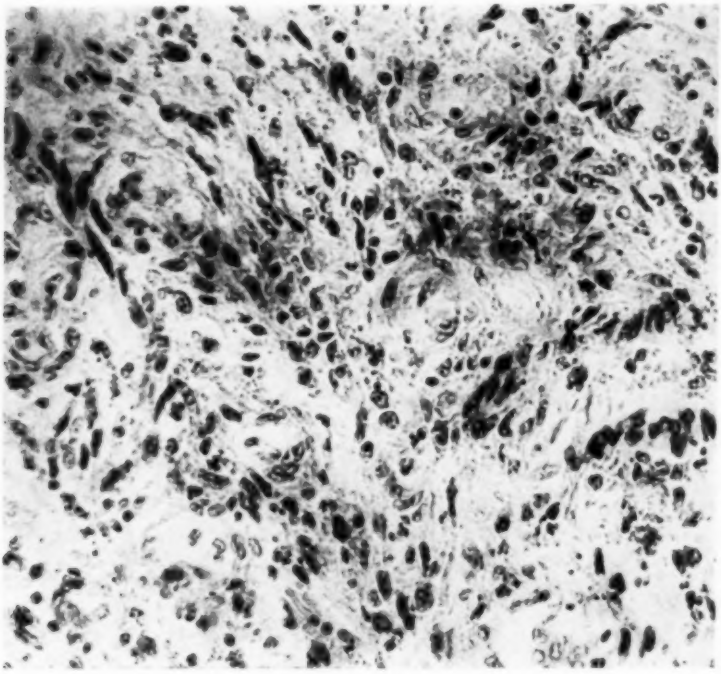

FIG. 4. Photomicrograph of the jejunal tumor. Spindle cells form miniature vascular channels. × 475.

COMMENT

Many authors in the past have debated the subject of the nature of the intestinal growths in Kaposi's disease. Some have contended that the intestinal masses were independent cancerous foci, whereas others have maintained that they represented true metastases from the skin tumors. In order to explain metastasis to the intestinal wall in the case herewith reported, one would have to invoke the concept of transpulmonic migration of tumor emboli without the setting up of discrete lung metastases. Willis [5] has stressed the fact that in true metastatic tumors of the bowel, the "blood-borne metastatic nature of the tumors is further attested by the almost invariable co-existence of multiple hemic metastases in other tissues." The known tendency of Kaposi's sarcoma to grow in the skin on the basis of multicentricity lends further support to the hypothesis

that the jejunal tumor had its origin in the blood vessels of the intestinal wall. Despite the foregoing arguments, it must be conceded that the axillary lymph node involvement does actually constitute metastasis from neoplastic tissue previously present in the right upper extremity.

SUMMARY

1. A case of Kaposi's sarcoma of 14 years' duration has been presented. In addition to the skin manifestations, the jejunum and axillary lymph nodes were also involved.

2. Perforation of the jejunal tumor caused generalized peritonitis and death. Such a complication has not been described heretofore.

3. Pathologic studies suggest that the jejunal sarcoma constitutes a site of origin independent of the skin involvement.

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A CASE OF MESENTERIC VENOUS THROMBOSIS WITH SURVIVAL *

By ALLAN M. GOLDMAN, M.D., F.A.C.P., and JAMES D. RIVES, M.D.,
New Orleans, Louisiana

THIS case is presented in the hope of contributing something of value to the literature on vascular accidents. From the history obtained it was difficult to estimate how long the mesenteric thrombosis had been present when the patient was first seen. The history was superficial owing to the condition of the patient and the inability of his wife to confirm the sequence of events.

CASE REPORT

The chief complaint was generalized, knife-like abdominal pain, radiating through to the back and most severe in the right lower quadrant. The patient, a 48 year old white male in the automotive accessory business, stated he had been having watery diarrhea for the preceding three weeks with occasional episodes of nausea and vomiting. Cramping abdominal pain was intermittent and no blood was noted in the

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six to eight daily stools. Hematemesis was likewise denied. The intake of food did not apparently intensify or relieve the abdominal distress.

The past history failed to reveal previous gastrointestinal disturbance. In December, 1943, he had been in an automobile accident and six months later began having epileptiform seizures at infrequent intervals. Because of these attacks he was admitted to Touro Infirmary in July, 1944, for observation. An encephalogram done at this time was negative except for slight dilatation at the third ventricle. The spinal fluid, blood Wassermann reaction, and blood chemistry were normal. Roentgenograms of the skull revealed a small triangular opaque foreign body in the soft tissues at the base of the nose just to the left of the midline. On discharge from the hospital he complained of frequent headaches. Close questioning elicited a history of hypertension of several years' duration. In April, 1945, he visited the Mayo Clinic for consultation, but no surgery was advised. Dilantin sodium recommended at the Clinic greatly reduced the incidence of his epileptic seizures.

When seen for the first time at home February 2, 1947, at 12:45 p.m., he was acutely ill, in evident shock, irrational, but able to answer some questions confirmed by his wife. Temperature 97 F.; pulse 160, weak; blood pressure 120 mm. Hg systolic and 110 mm. diastolic; respirations 20 per minute. Cyanosis of the lips and nail beds was noted. He appeared poorly nourished with some signs of recent weight loss. The skin was cold and moist. Examination of the head revealed slight, bilateral exophthalmos, but the eye grounds showed no exudates, hemorrhage, or papilledema. Partial dentures were noted. The heart tones were of poor quality, and a sinus tachycardia was present. The lungs were resonant to percussion, and no râles were found.

The abdomen was markedly distended, with board-like rigidity. It was flat to percussion, silent on auscultation, and a questionable mass could be palpated in the left side. Because of the rigidity it was impossible to elicit a fluid wave or shifting dullness. Tenderness to light palpation was marked, especially in the epigastric region. No abdominal, inguinal nor femoral hernias were apparent. Genitalia were essentially negative. Rectal examination revealed a normal prostate and no masses. The extremities were cold, but presented no evidence of recent embolism, thrombophlebitis, or phlebothrombosis. The peripheral vessels seemed moderately sclerotic on palpation. Neurological examination revealed a moderate weakness of the left side of the body, including the lower face, arm and leg. The tendon reflexes were bilaterally and symmetrically increased. There was a positive Hoffman's sign on the left. The patient's wife stated that since the automobile accident there had been a change in his personality. He had become careless and markedly irritable.

The patient was admitted to Touro Infirmary within 45 minutes of his first examination and treatment for shock was begun. The blood count and chemistry on admission was as follows: White blood cells, 26,990; neutrophiles, 90, with a marked shift to the left; lymphocytes, 6; monocytes, 4; hemoglobin, .102 per cent; red blood cells, 4,46,000; hematocrit, 50 per cent. Serum amylase: 73 units. Blood dextrose: 159 mg./100 c.c. Urinalysis: Albumin negative; sugar. Benedict's test, green; sediment: no casts or red cells. Only 35 c.c. of urine could be obtained, acid in reaction and orange yellow in color. Specific gravity: quantity not sufficient.

A flat plate of the chest and abdomen on admission was reported as follows: Examination of the chest revealed the heart, great vessel and hilus shadows to be within normal limits except for calcification in the left hilar glands. This was associated with a small round calcification in the left midlung field characteristic of a primary complex. The lungs otherwise were clear, and the diaphragm was elevated, but smooth and well rounded; the costophrenic angles were sharp. No subphrenic air was demonstrated. Examination of the abdomen in the erect and supine positions revealed the presence of some gas in the transverse colon as well as in a number of segments of small intestine which were scattered throughout the abdomen. Fluid levels were noted

in the small intestine, but the absence of any distention was against a diagnosis of intestinal obstruction. The properitoneal fat lines were noted, but indistinct, suggesting that there might be some fluid in the peritoneal cavity. However, the psoas muscle shadows were sharp, ruling out any hemorrhage in the retroperitoneal space. The presence of fluid levels in the small intestine brought up the question of mesenteric thrombosis, but the findings were not characteristic and a diagnosis would require correlation with clinical and other laboratory findings.

Electrocardiogram on admission revealed a sinus tachycardia, rate 150, with depression of the ST segment in Lead II. It was otherwise non-contributory. He was given 2,000 c.c. of glucose and 500 c.c. of blood by vein, at which time his blood pressure rose to 160 mm. Hg systolic and 100 mm. diastolic, and the pulse slowed to 110. A Levine tube, with continuous suction, was maintained from the time of admission. By 7:00 p.m., approximately five hours after admission, it was decided to take the patient to surgery.

Laparotomy was performed by one of us, J. D. R., and a massive venous mesenteric thrombosis was noted. There was no apparent cause for this accident. Approximately 11 feet of gangrenous small intestine with a margin of normal bowel was resected. An aseptic end to end anastomosis was performed and more than one liter of serosanguineous fluid removed from the peritoneal cavity. An additional 500 c.c. of blood were given in the operating room. The patient left the table in fairly good condition. Continuous oxygen was administered on return to his room and heparin therapy was begun by the intravenous route. The clotting time varied for the next few days between six and 28 minutes.

On February 3 the following blood chemistry was noted. Non-protein-nitrogen, 50; dextrose, 97; sodium chloride 471; prothrombin power, 10 per cent. Vitamin K, 10 mg., was given because of the low prothrombin. Fluid, electrolyte, protein and vitamin balance were maintained by the use of glucose and saline, intravenous amigen solution, blood transfusions, and large doses of parenteral vitamins daily. The blood type was AB. Rh positive. At no time during the first postoperative week did the temperature exceed 100.4° F. by rectum. On February 4 the icterus index was 100; Van den Bergh test gave a biphasic direct reaction; the cephalin flocculation was 2 plus; the prothrombin power was 68 per cent; non-protein nitrogen was 33, and the urinalysis revealed 35 to 40 red cells per high power field. The red cell count was 4,750,000 and the white blood count, 15,700, with 82 polymorphonuclears. The next day the icterus index was 120, and three urine examinations were negative for blood cells. Because of the progressive jaundice and the general condition of the patient it was decided to discontinue heparin therapy. A non-protein nitrogen taken at this time was 31. By February 7 the icterus index had dropped to 100; the serum proteins totaled 5.07 with 3.01 albumin and 2.06 globulin.

Because of marked abdominal distention and a continuing ileus the Levine tube was replaced by a Miller-Abbott tube which was advanced with the aid of a bedside roentgen-ray unit. Reports were as follows February 8, 1947: Examination of the abdomen with the bedside unit indicated that a Miller-Abbott tube had entered the proximal jejunum, which apparently lay in the right upper quadrant of the abdomen. Very little gas was seen in the stomach and in scattered small intestinal loops. The colon exhibited a normal quantity of gas in the descending portion and rectum. It was assumed that the abdominal distention was due in large measure to a collection of fluid. The possibility that the fluid might be within the intestine as well as in the peritoneal cavity could not be ruled out.

The general condition of the patient remained good except for the persistent ileus. Blood pressure readings ranged from 140 to 160 mm. Hg systolic and from 90 to 110 mm. diastolic. The pulse rate ranged from 88 to 120, but was consistently around 90. On February 10, 1947 the following roentgenographic report was rendered: Re-

examination of the abdomen indicated that although the Miller-Abbott tube was coiled in the stomach and duodenum, there had been no further advance of its tip. Gas was seen in slightly dilated loops of small intestine in the epigastrium and left hypochondrium, no other small intestinal coils being visualized. The large bowel, as partially outlined by its gaseous content, was normal in caliber, and could be followed

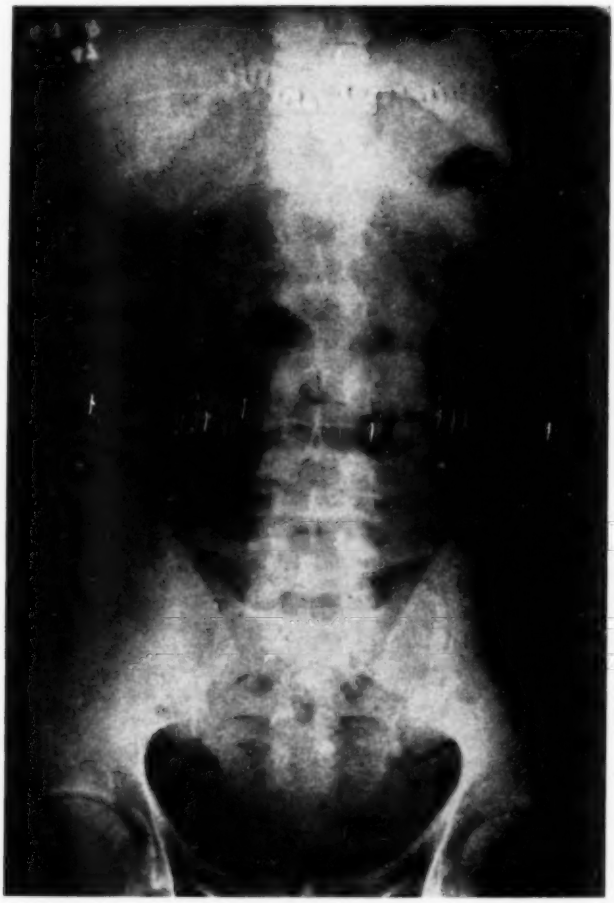

FIG. 1. Flat plate of abdomen taken on admission to hospital.

to the rectum. The presence of gas in the bowel beyond the tip of the tube indicated that it was not halted by mechanical obstruction, and further investigation after instillation of a small quantity of contrast material would be necessary to determine whether the delay in transport of the tube was due to incomplete obstruction (mechani-

cal), such as a kink, or whether it was due to atony. At this time the white blood count was 9,600 with 80 polymorphonuclears and the red blood cells 4.4 million.

The following day the abdomen appeared much less distended, and the patient retained all liquids with the tube clamped off. On February 12 the Miller-Abbott

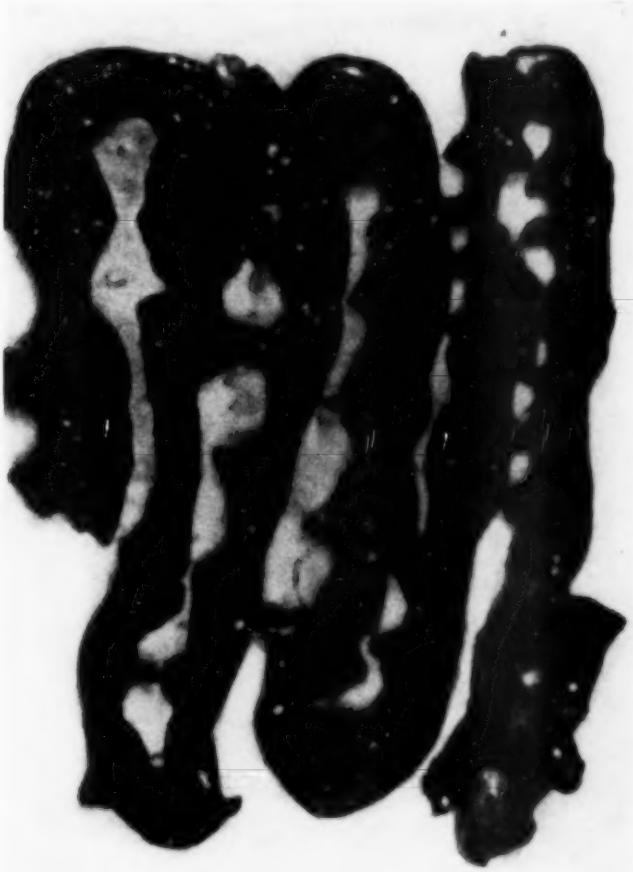

FIG. 2. Gross pathology. Section of gangrenous ileum removed at operation.

tube was removed and soft diet was begun. The icterus index at this time was 80. By February 15 he began passing liquid stools which were cultured and found to be negative for parasites. That day the icterus index was 60, but on February 17 the cephalin flocculation was 3 plus. Daily infusion and parenteral vitamin therapy were continued. At this time he was afebrile and remained so until the time of discharge.

One minor epileptiform seizure occurred February 14, 1947 and nitranitol with phenobarbital, two tablets three times a day, was given.

On February 20, 1947 the total proteins were 5.81 with globulin 3.26 and albumin 2.55. Intravenous daily serum albumin and plasma were given. Amino acids were given by mouth in the form of Nutragest, a palatable protein mixture. Low residue full diet was continued. By February 21 the icterus index was down to 30, and by

FIG. 3. Microscopic section of gangrenous ileum showing thrombosis of blood vessels.

FIG. 4a. Gastrointestinal series (see also figure 4b) taken prior to discharge from hospital.

February 24 the total serum proteins were 6.29, albumin 3.24, and globulin 2.95. Repeated stool examinations were negative for parasites and stool cultures were negative for pathogens.

There was no delay in wound healing but the patient continued to have cramping abdominal pain with alternating liquid and solid stools, three to five a day. Opium suppositories and Kaopectate-Opium mixtures were used with marked relief of symptoms. Frequent small feedings were taken, and the bowel seemed gradually to adjust to the disturbed physiology. On February 26, 1947 he was ambulatory and a gastrointestinal series was taken, with the following results: Fluoroscopic examination of the chest revealed no abnormalities. The contrast meal traversed the esophagus without difficulty. The stomach was of a J type and was displaced toward the midline by a

large spleen. The gastric walls were smooth and flexible, and peristaltic waves passed without interruption to the pylorus. No organic lesion was observed. The duodenal bulb filled immediately and was closely applied to the under surface of the liver, but apparently was smooth and regular. The distal duodenum was normal. Interval fluoroscopy of the small intestine indicated that practically all of the ileum

FIG. 4b.

had been resected, and end-to-end anastomosis performed between the distal jejunum and the remaining short ileal segment. Slight relative dilatation of the jejunum was attributed to mechanical obstruction of insignificant grade. At six hours the stomach and duodenum were empty, the barium being distributed through the lower small

bowel and colon, with the head of the column in the transverse. Fluoroscopy indicated that the terminal ileum and cecum were normal in contour and not unduly tender. The mobility of the cecum was somewhat limited.

The patient continued to improve from day to day, and the irritability of the bowel gradually subsided. Stools at times were well formed and on alternate occasions were liquid brown with no gross blood. The average number per day was three or four. The appetite was good, but at times the patient complained of mild abdominal cramping pain. Further examination in the form of proctoscopic study and barium enema had to be deferred because of the refusal of the patient to stay in the hospital. At the time of discharge March 2, 1947, moderate splenomegaly persisted, and the liver was enlarged 3 cm. below the costal margin. He was afebrile during the last two weeks' stay in the hospital.

Report of the pathologist was as follows: The specimen consisted of 435 cm. of small intestine (11.1 ft.), 255 cm. of which was gangrenous. The affected portion of this specimen was soft, thick walled, edematous and black in appearance. Thrombi were noticeable in the mesenteric vessels. The unaffected portion was dusty colored, somewhat edematous and grayish pink. The intestine was opened throughout its entire length and the mucosa of the affected portion was smooth and the lumen engorged with blood. Many of the small arterioles and venous capillaries presented necrotizing inflammatory reaction. It was not possible to determine whether this was primary or secondary. The larger vessels appeared patent. The conclusion was: Infarcted small bowel with gangrene, cause undetermined.

Subsequent follow-up of the patient at home during the month of March revealed him to be comfortable and ambulatory. The number of stools passed each day was reduced to a maximum of three. On March 11 sigmoidoscopic examination revealed a normal mucous membrane, and culture, zinc flotation, and direct smear examinations were negative for pathogens. By the end of March the spleen was barely palpable and the liver noted only on inspiration. He had gained five pounds and appeared to have completely recovered from the abdominal vascular accident.

A brief review of the literature reveals that mesenteric thrombosis is extremely rare in children, occurring most commonly in adults between the ages of 30 and 70 years. Males predominate over females, with the highest incidence in the fourth decade. At the Mayo Clinic up to 1938, Whittaker and Pemberton [10] report 60 cases, of which 57 came to necropsy. In 60 per cent of these the mesenteric vascular occlusion was unrelated to previous surgical procedure. The remaining followed operative procedures such as splenectomy, biliary or pancreatic procedures, appendectomy, or drainage of a gangrenous ruptured appendix, gastroduodenal operations, herniorrhaphy, operations on the transverse colon.

Superior mesenteric arterial occlusion was most common. Thrombosis was found following operation where conditions such as arteriosclerosis and splenic anemia existed. Embolus was associated with degenerative heart disease or with valvular disease. Lowance and Jones [7] report a case of mesenteric thrombosis in the presence of subacute bacterial endocarditis. Occlusion of the superior mesenteric vein occurs secondary to ascending thrombosis attributed to an infectious process such as appendicitis and pelvic infection. It also occurs secondary to descending thrombosis from the portal vein, with hepatic disease, or following abdominal surgical exploration.

In the series of Whittaker and Pemberton [10] a review of the pathology revealed vascular occlusion to be complete in each case studied. Thirty per cent of the cases had an associated thrombosis of the portal vein and 11.6 per cent

pulmonary emboli. In most cases there is a pregangrenous stage where the bowel wall is edematous, congested and with a deep red or bluish discoloration. The mesentery is dark, thickened and doughy as a result of hemorrhage. Infarction of the bowel is usually hemorrhagic in type, as had been shown by Dye [5] and others. When gangrene is present there is usually a bloody ascites and the bowel is distended with fluid. This is in contrast to the distention with gas seen in mechanical obstruction. Warren et al.[9] believe that the bloody ascites is probably a transudate from the congested, hemorrhagic infarcted bowel. The blood within the bowel has been noted. Peritonitis is commonly the end result of the process.

The symptoms and signs follow a sudden arterial occlusion or a more slowly progressive venous occlusion. The presenting symptoms are those of an abdominal emergency. Pain is sudden, severe and generalized with vomiting and abdominal distention. Either constipation or diarrhea may be present with blood in the stools. The signs of peripheral vascular collapse climax the picture.

The incidence of this condition is such that both the internist and surgeon should be on the alert for its presence. In the diagnosis, several important features are present. The white count generally exceeds 20,000, higher than in most acute abdominal conditions. A tense, silent abdomen with a fluid wave is suggestive of mesenteric thrombosis. Fluid in the small bowel on roentgenographic examination instead of gas is likewise indicative. Absence of air under the diaphragm speaks against a ruptured viscus. A normal serum amylase tends to rule out the diagnosis of acute pancreatitis. One of us, J. D. R., has been able to palpate a mass in three recent cases of mesenteric thrombosis prior to operation. The presence of a left sided mass in our case guided the surgical approach. In the presence of an acute myocardial infarction the upper abdomen may occasionally be tense, but offers little confusion. The rare rupture of an abdominal organ may at times simulate the picture of a vascular occlusion.

The prognosis of such a serious condition is not good and the mortality rate is high. The lesion is usually extensive and tends to progress. Immediate treatment of shock and early surgical exploraton with the postoperative use of anticoagulants offers the best chance for recovery. Fox [6] reported the use of Dicumarol in a case with gangrene of 60 cm. of the ileum with recovery. D'Abreu and Humble [3] reported a case of mesenteric venous thrombosis with recovery following surgery and the use of continuous heparin. They determined the amount of heparin to be given by the use of a heparin resistance test instead of the clotting time usually carried out. The titratable coagulability of the patient's blood was noted using heparin of diminishing strengths. This method seemed more accurate. Allen et al.[1] prefer heparin to Dicumarol in the presence of mesenteric thrombosis because of the difficulty in reversing the effect of the Dicumarol.

In summary we have presented a case of idiopathic mesenteric venous thrombosis. Interesting problems presented themselves in both the surgical and medical management of this case. The relative ease with which the gastrointestinal tract adjusted to the loss of such an extensive segment of small intestine is in keeping with previous reports. Fluid, protein, electrolyte, and vitamin balance were constantly watched in order to avoid any irreversible state. At present the patient is under constant observation and continues to improve.

Further search as to the cause of the idiopathic venous thrombosis is being carried out.

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ENDOCARDITIS CAUSED BY ORGANISM MORPHOLOGICALLY AND CULTURALLY IDENTIFIED AS *C. diphtheriae* *

By Bertram Zheutlin, M.D., *Ann Arbor, Michigan*

Corynebacterium diphtheriae characteristically affects the heart by producing a toxin which causes a myocarditis. Only in unique cases does the diphtheria organism directly affect the pericardium or endocardium. This report deals with a case in which endocarditis was caused by an organism resembling the Klebs-Loeffler bacillus morphologically and culturally, and which proved to be virulent for guinea pigs.

Case Report

A 19-year-old white enlisted man was admitted to the hospital May 26, 1946, with the chief complaints of sore throat, chilly sensations, and fever. The family history was non-contributory. The past history revealed that the patient had had good general health and strength until eight years before induction into the Army. The patient stated that in 1936 he had rheumatic fever followed by St. Vitus dance, following which he spent much of the last eight years in medical institutions. He had had the usual childhood diseases but no other significant infectious diseases. He did not know if he had had diphtheria immunization when a child, and he was not immunized against diphtheria while in the Army. The rest of the past history was not significant.

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Twenty hours before admission the patient had noticed chilly sensations, fever, and sore throat which progressively increased in intensity. There were no skin lesions, joint pains, chest pain, respiratory difficulty, or other pertinent complaints.

The physical examination at the time of admission revealed a mildly acutely ill white male who was in no distress. The tonsils were moderately edematous and red, and both were covered with small patches of gray membranous exudate. Heart and lungs revealed no significant abnormalities, and it is recorded that no cardiac murmurs were heard. The rest of the physical examination was reported as being within the range of normal.

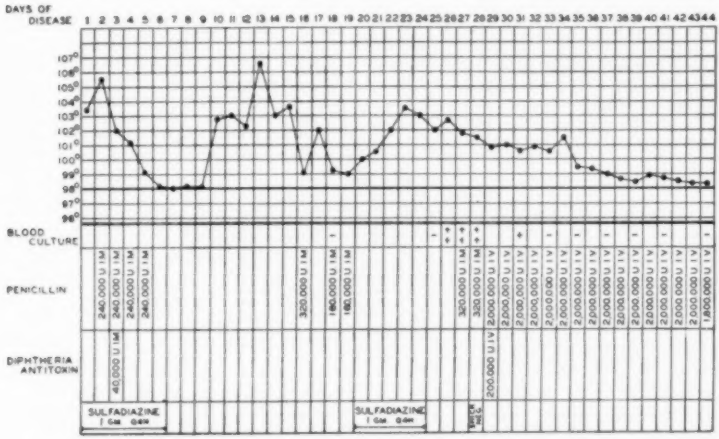
Urinalysis at the time of admission was negative for any significant abnormalities. The red blood count was 4,920,000, and the white blood count was 14,100 with a normal differential. Throat smears revealed organisms resembling *C. diphtheriae*, but culture and fermentation tests did not substantiate this. No Vincent organisms or beta hemolytic streptococci were demonstrated in the patient's pharynx. The patient was given penicillin, 30,000 units every three hours, and sulfadiazine, four grams initial dose and one gram every four hours. Because of the organisms resembling *C. diphtheriae* on the admission throat smear, the patient was given 40,000 units of diphtheria antitoxin, chiefly as a precautionary measure. He became afebrile by the fifth hospital day and penicillin was discontinued on the sixth hospital day. The sulfadiazine was discontinued on the seventh hospital day.

The patient continued afebrile until the tenth hospital day when, just before he was to be discharged to duty, he had a shaking chill and his temperature rose to 102° F. A roentgenogram taken at that time showed an area of haziness in the right midlung field suggestive of atypical pneumonia. The size and shape of the heart were recorded as being within normal limits.

The patient continued to have daily spiking temperatures reaching an average height of 103° F., and 106° F. on one occasion. On the sixteenth hospital day he was given 40,000 units of penicillin every three hours for eight doses, and it was noted that there was some decrease in the temperature. The highest it reached the following day was 100.4° F., a definite improvement over the previous five days. The temperature again started upward after penicillin was discontinued and the patient was again started on penicillin, 20,000 units every three hours. A blood culture taken at this time revealed no growth, but the value of the blood culture was limited because the patient was on penicillin and penicillin inhibitor was not used in the blood culture. Following the administration of penicillin, the temperature again showed a gradual decline, but for some reason penicillin was discontinued after 48 hours and on the nineteenth hospital day the patient was started on sulfadiazine, 4 grams stat and 1 gram every four hours. A roentgenogram of the patient's chest at this time, one week after the first film, showed no abnormalities in the heart or lungs. After the patient was changed over to sulfadiazine his temperature gradually increased and by the twenty-third day was again spiking daily to between 103° F. and 104° F. All this time blood studies revealed a red blood count within normal limits and a white blood count ranging between 10,000 and 14,000 with a normal differential.

On the twenty-fourth hospital day, one noted a well developed but poorly nourished white male who appeared chronically and critically ill, though in no immediate distress. He was drowsy and lethargic. There was evidence of much recent weight loss. There were petechiae on the right shoulder (posteriorly), the left lower conjunctiva, and on the medial aspect of both ankles. There was no cyanosis, jaundice, or other significant skin abnormalities. Ears, eyes, nose, throat, and neck were not remarkable. Lungs were clear to percussion and auscultation. Cardiac dullness percussed to the anterior axillary line, with the apex impulse and the point of maximal impulse localized just inside the anterior axillary line. The heart sounds were of fair quality and regular in rate and rhythm. There was a loud harsh apical systolic

murmur which was transmitted to the axilla and which was not affected by change in position and respiration. There was an early, short, harsh systolic murmur in the pulmonic area which varied with position and was not transmitted into the neck vessels. The second pulmonic sound was accentuated. A diastolic third heart sound could be heard at the apex when the patient was supine but disappeared when the patient rotated to either side. Over both ankles there was tenderness, heat, swelling, and redness. There were numerous petechiae over these latter areas. There was no lymph node enlargement and the spleen was not palpable. However, there was tenderness to palpation in the left upper abdominal quadrant. The rest of the physical examination revealed no pertinent abnormalities.



Sulfadiazine was discontinued, and the next day, the twenty-fifth hospital day, blood cultures were drawn at a time when the temperature was thought to be rising. During the next four days seven blood cultures were made, each one producing a heavy growth of pleomorphic gram positive bacilli, morphologically and culturally resembling *C. diphtheriae*. The organisms were cultured from the blood in the following manner: Three cubic centimeters of blood were put into brain heart infusion and para-aminobenzoic acid, 0.1 per cent, a medium prepared by Difco. The culture was observed for seven days and any growth noted during this time was subcultured to a blood plate. The organism grown in the brain heart infusion was a pleomorphic gram-positive rod resembling *C. diphtheriae* morphologically, and from the blood plate was transferred to Mueller's serum tellurite where colonies typical for the Klebs-Loeffler bacilli were produced. This type of medium inhibits the growth of cocci and diphtheroids and on it *C. diphtheriae* produces a characteristic colony distinguishable from *C. xerosis* and *C. Hoffmani*. Sugar fermentation tests identified the organism as belonging to the mitis strain.

To test the virulence of the organism after it was identified as *C. diphtheriae*, it was grown on brain heart infusion for 24 hours and a saline suspension containing approximately 900,000 organisms per cubic centimeter was made. One-tenth centimeter of this suspension was injected subcutaneously into a shaved area on the abdomen of a guinea pig. Three hours later 1,000 units of diphtheria antitoxin were administered intraperitoneally, and at another shaved area 0.1 c.c. of the saline suspension containing about 90,000 organisms was injected subcutaneously as a control.

The organisms injected before diphtheria antitoxin was given produced a necrotic lesion in 24 hours, whereas the organisms injected simultaneously with the antitoxin did not produce a lesion. This was considered to constitute a positive virulence test.

A test for the sensitivity of the organism to penicillin was somewhat inaccurate due to the lack of a standard organism of known potency, such as the standard Florey reference strain of staphylococcus; but brain heart infusion with a pH in the neighborhood of 7 was prepared in samples containing 20, 2, 0.2, 0.02, 0.01, and 0.002 unit of penicillin per cubic centimeter of broth. Growth was inhibited in the broth containing 0.01 unit of penicillin per cubic centimeter, and the organism was interpreted as being sensitive to penicillin.

The Schick test was negative on the twenty-ninth hospital day. An electrocardiogram unfortunately was not available at the time. Nose and throat cultures revealed normal flora, and the urine showed no abnormalities.

As soon as the identification of the organism and its virulence were definitely established penicillin therapy was instituted. The patient was given intravenous penicillin, 2,000,000 units every day in 2,000 c.c. of normal saline and glucose 5 per cent. Diphtheria antitoxin, 10,000 units every hour, was given intravenously for 20 hours, after which it was discontinued because of the appearance of many urticarial wheals. A total of 1 gram of digitalis was given during the next two days, followed by 0.1 gram of digitalis every day. Subtotal digitalization, the value of which is open to debate, was carried out because it was felt that, in addition to whatever beneficial effects the incomplete digitalization might directly accomplish on the action of the heart, the patient could be completely digitalized very rapidly if he showed signs of congestive failure. It was thought that these factors overweighed the danger of increased sensitivity of the heart to the toxic manifestations of digitalis in the presence of infection. In addition to the above specific therapy, the patient was also given intensive routine supportive therapy consisting of a high caloric diet, parenteral and oral vitamins, salicylates for the joint manifestations, and intravenous fluids.

Penicillin was continued for seven weeks. The first four weeks it was given in a continuous intravenous drip, whereas the last three weeks it was given intramuscularly every three hours. The first two weeks the patient received 2,000,000 units every day, and the third and fourth weeks the dose was gradually decreased from 2,000,000 units to 600,000 units daily by the continuous intravenous infusion. The fifth week he received 100,000 units every three hours intramuscularly, the sixth week 50,000 units every three hours intramuscularly, and the seventh week 40,000 units every three hours. A total of 55,440,000 units of penicillin was given, 44,800,000 units intravenously and 10,640,000 units intramuscularly. No untoward reactions were noted from the massive doses of penicillin given.

A blood culture taken two days after intravenous penicillin was started was positive for *C. diphtheriae*, but a blood culture taken on the thirty-third hospital day—four days after penicillin was started—was sterile, and blood cultures taken frequently thereafter were all sterile. The temperature gradually dropped; eight days after penicillin was instituted the patient's temperature was normal, and he has remained afebrile. Tenderness in the splenic area disappeared 10 days after intensive therapy was started, and no further evidence of embolic phenomena was seen after the forty-fifth hospital day, 14 days after intravenous penicillin was started.

The point of maximum cardiac impulse, which at the start of therapy was at the anterior axillary line, was localized inside the nipple line 15 days after the intravenous penicillin was started. Digitalis was discontinued after four weeks. Except for the disappearance of tachycardia and improvement in quality of the heart sounds, there was no change in the heart. The loud apical systolic murmur and evanescent systolic pulmonic murmur persisted and the mid-diastolic third heart sound was heard when the patient was supine.

During the patient's entire hospital stay, the red blood count ranged between 4.5 and 5 million, with the hemoglobin always above 90 per cent. The white cell count ranged between 10,000 and 14,000 with a normal differential. Repeated throat cultures and urinalysis never revealed any significant abnormalities. The Schick test, repeated several times, was negative.

At the time of writing the patient had not had penicillin for six weeks and had been out of bed for four weeks. Blood cultures had been sterile. The patient had been afebrile and there had been no evidence of embolic phenomena. The loud apical systolic murmur remained present and the third heart sound was heard while in the supine position but, as before, disappeared when the patient rolled to either side. It must be remembered that these cardiac findings were not present at the time of admission. The blood count and urinalysis were within normal limits. Subjectively the patient's condition was excellent, his appetite enormous, and he was rapidly regaining the weight he had lost. The patient was returned to the Zone of Interior, so further personal follow-up was not possible.

Summary

A case of endocarditis caused by an organism identified as *C. diphtheriae* is reported because of the extreme rarity with which the Klebs-Loeffler bacillus directly attacks the endocardium.

FATAL MERCURIALISM DUE TO PROLONGED INTRAVENOUS ADMINISTRATION OF A MERCURIAL DIURETIC *

By Maurice B. Siegel, M.D., and Alan J. Friedman, M.D.,
Los Angeles, California

The clinical use of organic mercurials to control the edema of congestive heart failure has had widespread clinical application since their introduction a generation ago.[1, 2, 3] These diuretics have had considerable usage also in the control of edema in the chronic nephritides, [3, 4] although some point out that their use should be contraindicated because of their nephrotoxic effects.[5, 6] In the case to be presented, mercupurin was used over a period of several months in doses ranging up to 4 c.c. twice weekly to control the edema of a young diabetic man with the syndrome of Kimmelstiel-Wilson. [7] The postmortem examination revealed changes in the kidneys and gastrointestinal tract which were definitely consistent with mercury poisoning and quantitative chemical examination disclosed a toxic amount of mercury in the involved organs.

Case Report

This 23 year old white male was first seen in the outpatient department of this hospital in 1937 for the treatment of his diabetes which had been present for the past 12 years. During this interim, the patient had been treated with insulin and diet.

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From the Division of Pathology, Cedars of Lebanon Hospital, Los Angeles, California.

At 14 years of age bilateral juvenile cataracts were removed. His blood pressure at his first hospital visit was 110 mm. Hg systolic and 74 mm. diastolic, and his physical examination was essentially normal with no evidence of cardiac enlargement, renal diseases, or diabetic retinopathy.

He was again seen two years later. Blood pressure at this time was 120 mm. Hg systolic and 100 mm. diastolic, and there was now also a history of occasional ankle swelling and dyspnea on effort. Physical examination again revealed no significant findings.

He was not seen again until January of 1941 when he was first admitted to this hospital for control of diabetes and medical evaluation. His condition was improved by a diabetic diet and insulin coverage and he was discharged to the outpatient department for follow-up care. This diabetic régime was checked regularly and changes were made whenever necessary. In general, his diabetes throughout was difficult to control. At this time, his urea clearance was 142 per cent of normal, his non-protein nitrogen was 30 milligrams per 100 c.c.,* and the urinalysis was negative for red blood cells, casts and albumin.

During 1942 there were four admissions to the hospital. In January the patient was treated for diabetic acidosis following an upper respiratory infection, at which time he was also treated for pyorrhea and pyogenic skin infections. Subsequent admissions were made for medical evaluation and diabetic control. Repeated urinalyses now showed a heavy trace of albumin. Incidental findings in roentgen-rays taken this year revealed absence of both frontal sinuses and calcification of the peripheral arteries. Blood pressure was 130 mm. Hg systolic and 85 mm. diastolic.

In 1943 there were three admissions to the hospital. The first was for massive hemorrhage into the vitreous of the right eye, resulting in almost complete loss of vision in this eye. Blood pressure at this time was 122 mm. Hg systolic and 98 mm. diastolic. There was almost total blindness, only light perception bilaterally being present. Albuminuria persisted with the additional finding of a few red blood cells per high power field in the urinary sediment.

In 1944 there were two admissions. There had been increasing loss of vision, and at this time the ophthalmologist made a diagnosis of bilateral diabetic retinitis (Grade IV, Wagener). In April of 1944, there was persistent albuminuria with a non-protein nitrogen of 38 mg. per cent. By the end of the year there developed edema over the lower extremities and sacrum. The non-protein nitrogen was now 70 mg. per cent and the creatinine 2.2 mg. per cent. Urea clearance was 46 per cent of normal, and an occasional hyaline and finely granular casts began to appear in the urine in addition to albumin and red blood cells. The specific gravity was now fixed at 1.012. The edema was controlled on low salt diet, bed rest and restricted fluids, but it never completely disappeared.

There were two admissions in 1945. The first was for an acute mastoiditis on the right side which was cured with penicillin. Hemoglobin which had previously been normal was now 70 per cent, with a red blood count of 3,800,000. The second admission was for acute congestive glaucoma of the right eye which was alleviated by paracentesis. Once again there was progressive edema of the lower extremities with partial remission on low salt diet, bed rest, and restricted fluids. Serum protein was decreased to 5.1 gm. per cent, serum albumin being 2.5 gm. per cent, serum globulin 2.6 gm. per cent, giving an A : G ratio of .96.

In 1946 there were three admissions to the hospital. His edema had persisted and there was now fairly marked dyspnea on mild exertion. Later there were anorexia and vomiting. In March 1946, his non-protein nitrogen was 51 mg. per cent. Serum albumin was 2.6 gm. per cent, serum globulin 2.6 gm. per cent. Hemoglobin was 73 per cent and urinalysis showed albumin, numerous red blood cells and occasional white

* Hereafter, to be designated as mg. per cent.

blood cells per high power field. At this time, in addition to the diabetic régime, low salt diet, bed rest, and restricted fluids, mercupurin in doses of 2.2 c.c. twice a week was instituted for the relief of the edema which was now extensive and interfered with his activity. This therapy was continued later in the outpatient department of this hospital and on subsequent hospital admissions for the remainder of his life. His edema persisted in spite of this therapy, and in the later months of his life he required larger doses (4.4 c.c. twice a week) intravenously in order to obtain effective diuresis.

FIG. 1. (× 60). Section of large bowel showing necrosis of mucosa with surface slough and polymorphonuclear infiltration.

On July 26, 1946, the patient was readmitted with anorexia, vomiting and persistent bloody diarrhea. There was now persistent anasarca despite the use of mercurial diuretics. Stool and blood cultures were negative. Blood pressure was 180 mm. Hg systolic and 120 mm. diastolic, non-protein nitrogen was 86 mg. per cent, creatinine 4.3 mg. per cent, serum albumin 2.4 gm. per cent, serum globulin 2.5 gm. per cent, and hemoglobin 63 per cent. The patient was given several blood transfusions and was discharged unimproved for follow-up care and further therapy in the outpatient department.

The final admission was on September 27, 1946. The anasarca had persisted as had his bloody diarrhea. Blood pressure was now 200 mm. Hg systolic and 125 mm. diastolic. During the last week there was no improvement in the edema, and the patient became stuporous and died on October 14, 1946. Terminally the blood urea nitrogen was 95 mg. per cent, creatinine 5.2 mg. per cent. The urine showed 4 plus albumin with 15 to 20 white blood cells per high power field, 20 to 25 red blood cells per high power field, and an occasional hyaline cast. It was felt that his rising azo-

FIG. 2. (× 300). Section of kidney cortex showing intercapillary glomerulosclerosis with hyalinization.

temia, hypoproteinemia, anasarca, and bloody diarrhea were all part of his progressive renal insufficiency.

Postmortem Examination. The autopsy was performed 14 and one-half hours after death. The following description will be limited to the significant findings.

The body presented a pronounced anasarca. The heart weighed 360 grams and the left ventricle was slightly hypertrophied. The lungs were moderately congested and edematous. Focal areas of atelectasis were noted. The liver weighed 2,240 grams

and showed considerable acute passive hyperemia. The kidneys each weighed 180 grams, which is somewhat heavier than normal. The external surfaces were smooth and pale. On section, the cortex was moderately thickened and the cortical striations were obscured. The blood vessels were not unduly prominent. The gastrointestinal tract was moderately distended with gas and hemorrhagic, semifluid fecal material. The wall of the large bowel was moderately thickened. The mucosa showed extensive ulcerations with considerable hemorrhagic discoloration. The pancreas was located with considerable difficulty. It was represented by small isolated masses of tan tissue

FIG. 3. (× 675). Section showing mitotic figure in regenerating tubule.

having the usual lobular architecture of pancreatic tissue. The total amount was estimated to weigh not more than 25 grams. The posterior halves of both eyes were removed for examination. The vitreous chamber contained irregular masses of semi-translucent and opaque grayish-white tissue. The normal structures were almost completely obliterated. The retina could not be identified. The choroid coat and the sclera showed nothing remarkable grossly. The other organs, including the brain, revealed no significant findings.

Microscopic examination of the large intestine revealed extensive necrosis of the mucosa, with ulceration and considerable edema of the bowel wall, as well as infiltration by inflammatory cells, chiefly polymorphonuclear leukocytes (figure 1). Sections of the kidneys disclosed several pathological findings. There was intercapillary glomerulosclerosis, as originally described by Kimmelstiel and Wilson.[7] Several of the glomeruli showed conglomerate spherical hyaline masses in the central portion of the capillary tufts. Other glomeruli showed partial or complete fibrosis and there was a marked reduction in the total number of preserved glomeruli (figure 2). The tubules

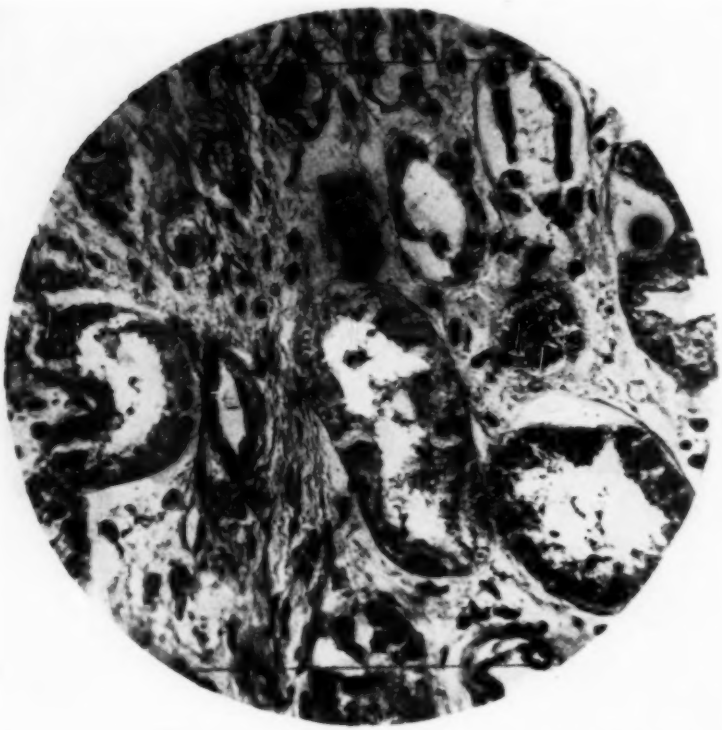

FIG. 4. (× 300). Section of kidney showing tubular necrosis and focal calcification.

showed considerable swelling of the cells, extensive granularity of the cytoplasm, and, in many places, loss of nuclear detail and cellular outline. Others showed a moderate amount of amorphous and granular acidophilic material in the lumens. Also seen were many tubules whose cells were larger and plumper than normal with compact cytoplasm, considerable variation in the size, shape and staining qualities of the nuclei, and occasional mitotic figures (figure 3), all of which suggested regenerating tubular elements. In addition, multiple foci of calcification could be seen scattered throughout the cortex, mainly involving tubular epithelium (figure 4). The arterioles and small

arteries also showed a considerable amount of sclerosis with medial and intimal thickening.

Microscopic examination of the eyes revealed a considerable distortion of the retina, with varying stages of degenerative change. There was considerable organizing blood clot in the vitreous chamber. The outer coats of the eye revealed nothing remarkable.

Because the hemorrhagic ulcerative colitis was too extensive to be adequately explained by the degree of azotemia, the possibility of mercurialism was suspected. Portions of the colon, stomach, kidneys and liver were subjected to toxicological examination.

The analysis for mercury was made by Dr. D. G. Simonson (Los Angeles County General Hospital). The following values for mercury were secured:

Colon	5.3 mg. of mercury per 100 grams of tissue;
Stomach	4.6 mg. of mercury per 100 grams of tissue;
Kidneys	3.2 mg. of mercury per 100 grams of tissue;
Liver	3.0 mg. of mercury per 100 grams of tissue.

The final anatomic diagnoses were as follows: Hypoplasia of the pancreas (with diabetes mellitus); intercapillary glomerular sclerosis (Kimmelstiel-Wilson's disease); cardiac hypertrophy, left ventricle; chronic mercurial poisoning, secondary to mercurial diuretics. The anatomical findings were consistent with the clinical diagnosis of hypertensve cardiovascular disease with cardiac failure and uremia.

Discussion

Kimmelstiel and Wilson, [7] in 1936, first described a nephrotic syndrome associated with hypertension and uremia complicating the course of diabetes mellitus. This was apparently attributable to sclerosis between the capillaries and the epithelium of the glomerular tufts. Siegal and Allen [8] reëxamined diabetic and arterial nephrosclerotic autopsy material and found the typical lesions in 33.3 per cent of diabetic kidneys, and in only 1 per cent of nephrosclerotic kidneys. Goodof [9] reviewed 214 cases of diabetes and found 44 per cent of his cases showed the lesions of intercapillary glomerulosclerosis. Thus these investigators felt that this entity was a separate disease syndrome clinically and pathologically. However, Bell [10] as well as Horn and Smetana, [11] has stressed the non-specificity of these lesions and declare that they cannot be made the basis for a pathological diagnosis of diabetes mellitus as they are frequently found in non-diabetics and arteriosclerotic kidneys.

This patient showed the clinical and pathological features which typify the Kimmelstiel-Wilson syndrome, and more, since the sclerosis also extended to involve the arterioles and larger arteries. He developed the hypertension, persistent albuminuria with a nephrotic picture, and the progressive azotemia with termination in uremia. Whether his rising non-protein nitrogen and creatinine, anasarca and bloody diarrhea are to be explained by the renal disease or the mercurial injury cannot be settled definitely, but since the mercury was present in toxic quantities associated with characteristic nephrotic changes, the mercury was undoubtedly a major contributing factor.

Bradley, [4] reviewing progress in Bright's disease, declares that mercurial diuretics are not detrimental to the kidney in the nephrotic phase and are very effective in establishing diuresis. Holman and Donnelly's experimental finding

that hypoproteinemia appears to protect the kidney in dogs may explain the infrequent occurrence of renal damage in nephrotic patients treated extensively with mercurial diuretics. [12] In our case, the patient received 138.8 c.c. of mercupurin intravenously over a five month period in doses ranging up to 4.4 c.c. twice weekly. Clinically one may well question whether continued mercurial administration is advisable in the face of a persistent and rising non-protein nitrogen and creatinine.

Saxl and Heilig,[13] in 1920, were among the first to advocate the use of mercurials as diuretic drugs and mercurous chloride (Calomel) was an integral part of the famed "Guys Hospital Pill." The precise mode of mercurial diuretic action has been a debated question, but the evidence points toward interference with tubular reabsorption of water as the modus operandi.[6] Recent studies by Reaser and Burch with radioactive sodium tracer doses show that mercurials increase excretion of the sodium ion.[14] This reduction in tubular reabsorption is apparently a result of the direct toxic action of the mercury ion on the tubular epithelium. Edwards [15] showed that mercury seems to exert its main effect on the midportion of the proximal convoluted tubular segment, rarely injuring the distal segment. Sollman, Schreiber, and Cole, [16] in their comprehensive work done in 1936, demonstrated that the ionizable inorganic compounds of mercury were the most potent diuretics, probably on the basis of the greater release of the mercury ion. Although these inorganic compounds are more efficacious diuretics, their greater tendency to toxic reactions led to their replacement by the newer organic mercurials. Mercupurin, N.N.R., is a chemical combination of mercurin and theophylline. The drug is marketed in a solution containing 39 mg. of mercury and 35.3 mg. of theophylline per cubic centimeter. In 1938, DeGraff, Batterman, and Lehman [17] showed that the principal action of the theophylline was to increase the rapidity and completeness of absorption of the mercurin, thus indicating that the diuresis obtained with this drug is primarily a function of the mercury in the mercurin fraction. The excretion of mercury begins immediately after administration, with the excretory function being handled almost entirely by the kidney and colon. The drug is most highly concentrated at the site of excretion and most of it is excreted within one to six days although traces may be detectable for months after administration. [6] Gold, [18] on the other hand, claimed that practically all injected mercupurin is excreted in 24 hours, and hence daily usage is permissible if necessary.

In a comprehensive review of the literature up to 1942, de Graff and Nadler [19] concluded that the systemic toxic reaction to the mercurial diuretics could be separated into two categories: those secondary to the diuresis rather than the diuretic, and those resulting from the drug itself. It was their contention that the reactions secondary to the diuresis could be eliminated by proper attention to the physiological control of electrolyte and water balance, since it was the derangement in these essential fields of homeostasis that led to the ill effects from increased and excessive urinary output. They found that the vast majority of toxic phenomena traceable to the mercurial itself manifested themselves through signs of gastrointestinal or renal disturbances. The most commonly encountered gastrointestinal symptoms were stomatitis, excessive salivation, or hemorrhagic colitis. The signals of renal involvement appeared in the following order: casts, albumin, leukocytes, and erythrocytes. The vast majority of reactions reviewed

by these authors were examples of drug idiosyncrasy or anaphylaxis since the toxic signs became evident immediately following one or two doses of the mercurial. In 1933 Rosenthal [20] reviewed the autopsy findings on the case of a 59 year old male who died two days after receiving his second dose of Salyrgan with a clinical picture strongly suggesting a marked drug sensitivity. Postmortem examination revealed marked hemorrhagic and inflammatory changes in the colon and changes in the kidneys suggestive of a nephrosis. Tyson [21] and Brown et al.[22] also described anaphylactic deaths following mercurials and described tissue changes essentially similar to those given above by Rosenthal.[20] They concluded that there was no correlation between the dosage of the mercurial and the pathologic change in the tissues. Waife and Pratt [23] recently reviewed a case of fatal mercurial poisoning following prolonged administration of Mercurophylline. The clinical story was that of a 35 year old white female who received Mercurophylline over a six month period for the relief of edema secondary to the congestive failure of old inactive rheumatic heart disease. Autopsy findings after a uremic death were essentially the same as those described by Rosenthal, the reportable feature of their case being the long term administration of the drug as contrasted to the quicker anaphylactoid phenomena recorded in most previous reports. Whereas the above represent immediate or delayed toxic fatal results of mercurial administrations, many reports current in the literature cite examples of safe usage of these drugs over prolonged periods of time with continued effectiveness.[19] Leaman cites a patient receiving 437 injections of mercupurin over a five and one-half year period, and at postmortem examination no gross or microscopic evidence of renal injury was seen.[24]

As noted under the autopsy findings above, the various tissue concentrations of mercury ranged from 3.0 to 5.3 mg. per 100 grams of tissue. The question might be raised as to what if any tissue concentration of mercury or evidence of kidney damage would be found in patients getting mercurials over long periods of time prior to death. The biochemist [25] who performed these tests has made similar mercury determinations on routine necropsy tissues of patients who were treated with mercurials but who died of postoperative myocardial infarctions or from cerebrovascular accidents and found that, if no kidney impairment was present, only minute traces of mercury could be recovered. The renal tubular lesions of focal calcifications and necrotizing nephrosis, with signs of regeneration, are rarely, if ever, seen in other types of renal disease in man. Goldblatt [26] considers that the latter two findings, i.e., focal calcification and regeneration of tubular epithelium are practically pathognomonic of mercurial injury to renal tubular epithelium in man.

Conclusion

As far as we can determine, this is the first reported case of fatal mercurial poisoning as a result of the administration of a mercurial diuretic, with quantitative determinations of the mercury content of the body tissues directly affected by mercury. Waife and Pratt [23] cited in their case report only qualitative determinations of mercury in the tissues, and whether or not it was present in toxic quantity is unknown. The quantities of mercury identified in our patient's tissues (obtained by duplicate determinations) are sufficiently high to represent lethal concentrations and are comparable to those usually seen in suicidal or accidental mercury poisoning.

The literature is replete with accounts of safe usage of mercurials and contains ample reports of drug anaphylactic reactions and reactions due to profuse diuresis with electrolytic disturbance.[19] However, the systemic poisoning by prolonged mercury administration has not been stressed to any degree by previous reports as it has always been felt that mercury is rapidly excreted and not stored in the body tissues or fluids to any appreciable extent. We now feel that the possibility of toxic mercurialism must be considered in the long range management of patients with chronic edema especially if azotemia is present and progresses under therapy.

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EDITORIAL

IMMUNOLOGIC STUDIES IN RHEUMATIC FEVER

DESPITE intensive investigation the etiology of rheumatic fever remains obscure. Important evidence has been accumulated, however, concerning a variety of contributory factors. Thus, it is generally agreed that the disease occurs more commonly under cool, damp climatic conditions than in warm, dry climates.[1] Epidemiologic data also permit the generalization that a poor economic status with its corollaries of overcrowding and undernutrition provides a more fertile soil for the development of rheumatic fever than the antithetical situation.[1] In addition to such external factors, careful students of the subject now firmly believe that the susceptibility to rheumatic fever is inherited as a single autosomal recessive factor.[2] The fact that not all genetic susceptibles inevitably develop rheumatic fever is explained by reference to the phenomenon of "penetrance." The latter term, widely used in genetics, refers to the varied somatic expressions of a single gene. Although the determinants of genetic penetrance are but poorly understood there is no doubt that associated diseases, age, and other factors are of importance.

In a disease problem of the magnitude of rheumatic fever the absence of an etiologic basis acts as a constant stimulus for further investigation. Many investigations, even though productive of negative results, have nevertheless permitted the closing off of one avenue of research and the concentration on other approaches. Present opinion, based upon a host of careful studies, that the lesions of rheumatic fever are not due directly to bacterial invasion exemplifies such an accomplishment.[3] Nevertheless, a close association with bacterial infection is clearly recognized. The nature of this association will be examined in some detail.

Evidence for a special relationship of Group A hemolytic streptococcal infection to rheumatic fever rests upon two imposing bodies of data, one group, epidemiologic, the other, immunologic. Paul has recently succinctly phrased the former relationship—"a 'good' year for hemolytic streptococcal infection is a 'good' year for rheumatic fever."[4] Recent studies at various Army posts have produced additional evidence in support of this view.[5] The relationship, although statistically significant, is by no means clear cut. No one type of streptococcus has ever been repeatedly incriminated as preceding episodes of rheumatic fever.[5] Furthermore, some studies

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have demonstrated that a proportion of attacks of acute rheumatic fever may not be preceded by clinically or culturally demonstrable streptococcal infection.[6]

Immunological evidence linking streptococcal infection with rheumatic fever has centered about the serologic demonstration during various phases of the disease of a variety of antibodies either to the entire bacterial cell, certain of its fractions, or various products of the organism.[7] The ubiquity of hemolytic streptococci and the fact that they may exist in the human host at times without producing clinical evidence of infection renders the interpretation of such immunologic findings in rheumatic fever somewhat hazardous. Much of the effort expended in this direction has been productive of either negative or inconclusive results. Thus the measurement of anti-streptococcal agglutinins showed comparable titers in a series of patients with active rheumatic fever as well as in a group of patients with acute streptococcal infections unassociated with manifestations of rheumatic fever.[8] Precipitin tests with the type-specific M protein and the C carbohydrate have likewise yielded inconclusive results.[7] Since the early thirties much interest has centered about the detection and measurement of antibodies against the streptococcal products, fibrinolysin and hemolysin (streptolysin). These studies, by and large, have also yielded results which merely emphasized again the relationship between streptococcal infection and rheumatic fever but which were more indicative of the preceding infection rather than pathognomonic of the latter.

The search for other varieties of streptococcal antibodies in the sera of patients with acute rheumatic fever still continues. Typical of recent investigations are the studies of Harris et al. on streptococcal anti-hyaluronidase.[8] In these studies two recent avenues of investigation show some tendency to merge. Considerable interest has been recently displayed in the subject of hyaluronic acid and its enzyme hyaluronidase.[9] Hyaluronic acid, a mucopolysaccharide, is believed to be an important constituent of the amorphous ground substance of connective tissue. Its presence has been demonstrated in the skin, synovial fluid, mesenchymal tumors, vitreous humor and umbilical cord. Hyaluronic acid is likewise known to be present in the capsular substance of streptococci. The term, hyaluronidase, is actually a collective one and denotes a variety of enzymes which have been obtained from divergent sources. Most Group A hemolytic streptococci produce hyaluronidase. Since the basic lesions of rheumatic fever are essentially in connective tissue, the possibility that an enzyme elaborated by streptococci may produce

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[9] Meyer, K.: The biological significance of hyaluronic acid and hyaluronidase, Physiol. Rev., 1947, xxvii, 335.

injury to the amorphous ground substance has been considered. It should be emphasized that this relationship is still a matter of speculation. Harris et al.,[10] and Friou and Wenner [11] were able to demonstrate a significant elevation in titer of an anti-hyaluronidase in the blood of patients with acute rheumatic fever. The degree of elevation observed in a series of patients with rheumatic fever was considerably greater than that observed in patients with other streptococcal infections. Furthermore, recurrence of activity was said to have been more often associated with a rise in anti-hyaluronidase titer than with other antibody titers. There was however no striking correlation between the titer and the severity of the illness. It remains yet to be determined whether this immunological change is simply another in the long list of immune reactions to streptococcal products or whether it has some special significance.

The idea that the lesions of rheumatic fever may represent a reaction of hypersensitivity has been held for a number of years.[12] Within recent years this concept has received further support—particularly with reference to the possibility that the tissue damage may be due to the action of auto-antibodies. Coburn [13] suggested that the reaction of the host in rheumatic fever may be divided into three phases. Phase I, which may last for 2 to 7 days, is predominantly characterized by signs of an upper respiratory infection and the presence of hemolytic streptococci in the throat. Phase II, a period of clinical quiescence of some 7 to 21 days, is associated chiefly with the beginning rise in titer of anti-streptolysin and the presence of a substance, termed by Coburn a precipitinogen, in the patient's serum. Phase III represents the first cycle of acute rheumatic fever and is characterized by the clinical aspects of the disease as well as by an increased titer of anti-streptolysin and the presence of a precipitin active against the precipitinogen of Phase II. The nature of the "precipitinogen" and "precipitin" have not been established. Coburn observed that the precipitin could not be absorbed by killed hemolytic streptococci of the strain infecting the patients. Cross precipitation between patients in this group was possible. The possibility that the precipitinogen of Phase II was an antigen formed by the conjugation of human protein and some streptococcal substance was considered. The precipitin of Phase III would represent the noxious agent, i.e., an auto-antibody capable of inducing tissue injury through its ability to react with the original undenatured or uncombined tissue protein. These studies have not yet been

[10] Harris, T. N., Harris, S., and Nagle, R. L.: Studies in the relation of the hemolytic streptococcus to rheumatic fever. VI. Comparison of streptococcal anti-hyaluronidase with antibodies to other streptococcal antigens in the serum of patients with rheumatic fever and acute streptococcal infection. Mucin clot prevention test, Pediatrics, 1949, iii, 482.

[11] Friou, J. J., and Wenner, H. A.: On the occurrence in human serum of an inhibitory substance to hyaluronidase produced by a strain of hemolytic streptococcus, Jr. Infect. Dis., 1947, lxxx, 185.

[12] Swift, H. F.: Rheumatic fever. Hektoen Lecture, Billings Foundation, Jr. Am. Med. Assoc., 1929, xcii, 2071.

[13] Coburn, A. F.: Rheumatic fever problem. I. Present status. II. Approaches awaiting development, Am. Jr. Dis. Child., 1945, lxx, 339 and 348.

confirmed. The Wedums [14] demonstrated that precipitins of the same type could be found in several diseases but less frequently than in rheumatic fever.

Although the concept of auto-antibody formation as a pathogenetic mechanism in rheumatic fever remains to be confirmed, further evidence of a supporting nature may be cited. Cavelti [15, 16, 17, 18] has demonstrated that rabbits and rats injected with homologous kidney substance plus streptococcal substances developed antibodies to plain kidney of their own species. In the rats it was found that as a result of the procedure inflammatory lesions resembling glomerulo-nephritis were produced. In further experiments Cavelti injected rats with streptococci plus extracts of rat heart, rat skeletal muscle and rat connective tissue. These animals developed antibodies to the respective tissues and were found on histological examination to have developed lesions of the valves and other connective tissue structures of the heart resembling "in a broad sense" those of rheumatic fever. In additional studies of rats focally infected with Group A hemolytic streptococci, autogenous tissue antigens appeared to be released into the blood stream during the height of infection and subsequently auto-antibodies to rat tissue were found. Carrying this work over to humans, Cavelti [19] prepared an antigen consisting of saline extract of normal human heart adsorbed upon collodion particles. The sera of 47 of 67 patients with active rheumatic fever produced agglutination of this antigen. Twelve normal persons displayed no antibodies and in a group of 84 patients with other diseases 1 weak and 3 doubtful positive reactions were obtained. Cavelti was unable to repeat these results in subsequent studies.[20] Repetition of these studies, perhaps by other immunologic technics, seems desirable.

Rich [21] has recently offered additional evidence in support of the concept of rheumatic fever as a reaction to hypersensitivity. Lesions resembling periarteritis nodosa were produced in experimental animals in whom serum sickness reactions had been induced by the injection of sterile horse serum or

[14] WEDUM, A. G., and WEDUM, B. G.: Serum precipitation reaction in rheumatic fever and in other conditions, Proc. Soc. Exper. Biol. and Med., 1946, lxi, 432.

[15] CAVELTI, P. A., and CAVELTI, E. S.: Studies on the pathogenesis of glomerulo-nephritis. I. Production of auto-antibodies to kidney in experimental animals, Arch. Path., 1945, xxxix, 148.

[16] CAVELTI, P. A., and CAVELTI, E. S.: Studies on the pathogenesis of glomerulo-nephritis. II. Production of glomerulonephritis in rats by means of auto-antibodies to kidneys, Arch. Path., 1945, xl, 158.

[17] CAVELTI, P. A., and CAVELTI, E. S.: Studies on the pathogenesis of glomerulonephritis. III. Clinical and pathological aspects of the experimental glomerulonephritis produced in rats by means of auto-antibodies to kidney, Arch. Path., 1945, xl, 103.

[18] CAVELTI, P. A.: Studies on the pathogenesis of rheumatic fever. I. Production of auto-antibodies to heart, skeletal muscle, and connective tissue in experimental animals, Arch. Path., 1947, xliv, 1. II. Cardiac lesions produced in rats by means of auto-antibodies to heart and connective tissue, Arch. Path., 1947, xliv, 13.

[19] CAVELTI, P. A.: Auto-antibodies in rheumatic fever, Proc. Soc. Exper. Biol. and Med., 1945, lx, 379.

[20] KERR, W. J.: Pathogenesis of rheumatic fever, Ann. Int. Med., 1948, xxix, 587.

[21] RICH, A. R.: Hypersensitivity in disease with especial reference to periarteritis nodosa, rheumatic fever, disseminated lupus erythematosus and rheumatoid arthritis, Harvey Lect., 1946–47, xlii, 106.

egg albumin. In the hearts of these animals lesions resembling rheumatic carditis were observed. In these experiments, therefore, an anaphylactic reaction seemed clearly to be the cause of the cardiac lesions. These and other investigations merely offer support for the pathogenetic concept, i.e. tissue injury of a characteristic type by anaphylactic reaction, rather than for any specific etiologic agent in rheumatic fever. The principle is an important one with potentially broad application. Additional examples of auto-antibody formation as a pathogenetic mechanism come from a variety of sources. One may cite the studies of Woods [22] on the etiology of sympathetic ophthalmia and Morgan's [23] work on the production of sensitization to brain tissue and encephalomyelitis by injections of homologous brain tissue.

Research in the etiology of rheumatic fever has been marked more often by failure than by success. Objective, unbiased, and repeatable data must support any theoretical concept. Such conclusive data have not yet been offered in support of any experimental approach to the problem. Immunologic studies offer not only an opportunity for clarification of basic etiological mechanisms but also an approach to a more exact diagnostic tool.

M. S. S.

[22] Woods, A. C.: Allergy and immunity in ophthalmology, The Johns Hopkins Press, Baltimore, 1933.

[23] Morgan, I. M.: Allergic encephalomyelitis in monkeys in response to injection of normal monkey nervous tissue, Jr. Exper. Med., 1947, lxxxv, 131.

REVIEWS

Fundamentals of Internal Medicine. By WALLACE M. YATER, A.B., M.D., F.A.C.P. 1451 pages; 17 × 25.5 cm. 3rd Ed. Appleton-Century-Crofts, Inc., New York. 1949. Price, $12.00.

This is an excellent and unusual textbook. It is intended primarily for the student and general practitioner—"to make readily available in simple form the essentials of the vast subject of internal medicine." This purpose is admirably achieved. The book is both compendious and comprehensive, and the authors, for the most part, have succeeded in combining a terse and business-like style with easy readability.

Innovations since the last edition include nearly 250 more pages; an increase in the number of contributing authors from 14 to 19; a detailed index at the beginning of each section; and the exclusive use of metric weights and measures. Two new and excellent chapters have been added, one on Chemotherapy and Therapy with Antibiotics, and one on Inhalational Therapy. The section on Electrocardiography has been expanded from a very inadequate dozen pages in the last edition to a scholarly thesis of some 50 odd pages. Unipolar leads are described and discussed in detail. Excellent as this section is, it far exceeds the bounds of the senior author's expressed purpose "to present the minimum amount of knowledge a medical student or general practitioner should have at his fingertips."

It is surprising to find that the concept of hypersplenism is practically ignored, and that the syndrome of acute focal nephritis is inadequately described. Again, the section on Medical Problems Incident to Flying is wordy and disproportionate, and all readers will not find the simultaneous treatment of acute and subacute bacterial endocarditis a happy experience.

While thoroughly up to date in therapy, the author does not "go overboard" after new remedies. Treatment sometimes tends to be sketchy, however, and it is noticeable that, for example, there is no mention of paludrine in malaria, hyoscine in seasickness or helium and oxygen in asthma.

In an authoritative textbook of this kind it is unfortunate to find terminological inaccuracies. As Somerset Maugham reminds us "words are tyrannical things, they exist for their meanings." It is therefore a pity that the misnamed syndrome, Erythromelalgia of the Head, is again invested with the sanctity of print. Such a title can only mean "painful red limbs of the head," which is anomalous to say the least. Again, under the heading Melena, no stretch of color vision can tolerate the inclusion of bright red bleeding. The misspelling of Achrestic, in both title and index, is minor but equally inaccurate.

A feature of this book is the valuable chapters on practical problems that the practitioners must daily face, but which are accorded too little attention in most textbooks and medical schools. Such are the sections on the Home Care of Patients with Contagious Diseases, Dietetics, and symptomatic and Supportive Treatment. In his final chapter, on The Physician Himself, Dr. Yater gives practical information and sound advice on many ethical and other questions which confront every doctor.

Other good features are the abundant illustrations, and the inclusion of tables of practical value (such as one comparing the cardiac glycosides, one on recommended therapy in infections, and several on the differential diagnosis of various disorders). A list of recommended texts is appended at the end of each section, and a section is devoted to Clinical Values and Useful Tables. In fact this book combines the good points of many others, for it is unusual to find so many excellent features and so much information in one volume of this size.

As a textbook and work of reference, this book can be recommended with confidence to students and practitioners.

H. J. L. M.

Coronary Artery Disease. By ERNST P. BOAS, M.D., Associate Physician, Mount Sinai Hospital, New York City, New York, and NORMAN F. BOAS, M.D. 399 pages; 14 × 20.5 cm. The Year Book Publishers, Inc., Chicago, Illinois. 1949. Price, $6.00.

This book summarizes much of the current knowledge concerning coronary artery disease. The sections on the anatomy, embryology, physiology, and pathology of the coronary arteries are excellent. The clinical portions of the book contain a wealth of detail concerning both typical and unusual features of coronary disease, and reflect extensive experience.

The authors' clinical classification of coronary artery disease is of particular interest. They "distinguish between simple angina pectoris and coronary insufficiency; because the former is of brief duration and causes no injury to heart muscle, whereas the latter is more prolonged and may be followed by varying degrees of myocardial damage. (The former) has typical anginal pain but no physical, roentgen, or electrocardiographic evidences of coronary disease." "Angina pectoris is a symptom complex . . . provoked by a sudden temporary inadequacy of the blood supply to a portion of the myocardium . . . it is . . . a form of coronary insufficiency." "Every attack of angina pectoris is due to transient coronary insufficiency." "Coronary insufficiency is a classification of convenience, not a clinical entity." In angina, "the pain rarely lasts more than three minutes, and the longest duration is ten minutes."

In "transient coronary insufficiency, as seen in a typical attack of angina pectoris . . . within half an hour at most the electrocardiogram returns to its original pattern." "Only when the tracing reverts to its original contour within an hour or so can we speak of transient coronary insufficiency."

"Acute coronary insufficiency is precipitated by some definite cause such as overexertion, shock, or hemorrhage." In "coronary insufficiency without myocardial infarction . . . the anginal pain may last half an hour or so and may be accompanied by sweating, pallor, drop in blood pressure. The electrocardiogram usually shows changes . . . and, at the latest within twenty-four hours . . . returns to normal. During the following days (there is) no fever, leukocytosis or acceleration of the sedimentation rate." In "acute coronary insufficiency with myocardial infarction . . . there is severe, prolonged anginal pain with or without shock, sweating and anxiety. After twenty-four hours or so . . . fever, leukocytosis, accelerated sedimentation rate."

"Coronary artery occlusion may be diagnosed if a patient experiences a severe, prolonged anginal seizure while at rest, without the intervention of any factor that might induce coronary insufficiency or a severe strain on the circulatory apparatus." In "coronary artery occlusion without myocardial infarction the symptoms are those of a severe attack of angina pectoris . . . that came on vicariously. In an hour or two . . . the pain subsides and evidence of shock disappears. . . . No fever or leukocytosis develops, the sedimentation rate . . . remains normal and no abnormalities are demonstrable in the electrocardiogram."

In coronary occlusion with myocardial infarction, "in milder cases the pain subsides in twenty to sixty minutes and does not return . . . (and) . . . the blood pressure may not be reduced. . . . More often (the pain) continues for hours up to forty-eight hours and the blood pressure usually falls." "Leukocytosis invariably follows a myocardial infarction." . . . "Fever is a constant sequel of myocardial infarction." ". . . the more carefully one inquires about the circumstances accompanying the onset of cardiac infarction, the more often does one discover an unusual or violent physical strain that initiated the symptoms."

The sections on treatment and differential diagnosis are timely and complete. The authors discuss the problem of whether or not physical exertion can induce myocardial infarction or coronary occlusion, and conclude that this sequence of events is by no means uncommon.

S. S.

Syphilis: Its Course and Management. By EVAN W. THOMAS, M.D., Professor of Clinical Medicine, New York University College of Medicine; Director, Rapid Treatment Center and Visiting Physician, Bellevue Hospital, New York; Consultant, United States Public Health Service. 317 pages; 16 × 24 cm. Macmillan Company, New York. 1949. Price, $5.50.

Dr. Thomas has presented a text which provides an understanding of the various stages of syphilis as far as our present day knowledge permits. There are 16 chapters which include the etiology of syphilis, its course, interpretation of the serologic tests, principles of treatment, methods of diagnosis of the various stages of syphilis and finally an excellent chapter on the public health aspects of the disease. The author's style is easy to follow and the wording is simple. The subject matter is adequately covered.

The author does not depend upon the statistics of others, but answers questions in the light of his own experience. For this he is well qualified. From the standpoint of a knowledge of the diagnosis of syphilis, the course of the disease and its treatment, this book is a valuable addition to the literature.

H. M. R., Jr.

Industrial Fluorosis: A Study of the Hazard to Man and Animals Near Fort William, Scotland. A Report to the Fluorosis Committee, Medical Research Council Memorandum No. 22. 131 pages; 15.5 × 24.5 cm. His Majesty's Stationery Office, London. 1949. Available from British Library of Information, 50 Rockefeller Plaza, New York. Price, 4 s. 0 d. net.

This report was issued by the Medical Research Council on the recommendations of their Fluorosis Committee to determine any effects of exposure to fluorine compounds on workers employed in factories manufacturing aluminum by an electrolytic process, and also to determine any effects upon those living in the neighborhood of such factories.

The paper-bound volume is divided into five sections and a summary as follows: Studies of contamination from the standpoint of topography, geology, meteorology, etc.; the effects of fluorine compounds upon animals in the area; clinical, radiological, hematological and biochemical findings in selected groups of individuals living in the area; the dental condition of adults and school children in the Fort William area; physical properties of bone in fluorosis. Each section was contributed by special workers. The volume contains 13 plates and 3 maps. The appendix includes an extensive review of the literature dealing with the toxicity of fluorine compounds and details of analytical methods.

From the mass of data collected, certain general conclusions are of interest. Workers from furnace rooms, where concentrations of fluorine as high as 3.6 mg. per cubic meter were encountered, inhale considerable quantities of fluorine. The excretion of fluorine in their urine roughly parallels the intensity of exposure. Workers exposed for a number of years to these conditions show bone changes of the type now generally recognized to be produced by fluorosis. Despite these changes none of the workers examined was found to suffer clinical disability. The recommendations of the Committee, however, are that determined efforts be made to reduce the fluorine exposure. The hazards to the surrounding population appear to be slight but con-

stitute a potential danger. The effects on animal husbandry constitute a serious impediment to farmers in the area.

C. J. C.

Child Psychiatry. (Enlarged second edition.) By LEO KANNER, M.D., with prefaces by JOHN C. WHITEHORN, M.D., ADOLF MEYER, M.D., LL.D., and EDWARDS A. PARK, M.D. 752 pages; 16 × 26.5 cm. Charles C. Thomas, Springfield, Illinois. 1949. Price, $8.50.

This edition has been entirely rewritten and is a great improvement over the 1935 edition. The field of child psychiatry is a relatively new field, and many advances have been made since 1935. For this reason an up-to-date revision of this important work is very welcome. As with most textbooks in medicine, this volume is not designed so much for the specialist in the field as it is for those who want to learn something about the subject. It is particularly useful to pediatricians who wish to learn how to treat the emotional problems of the children they see. It is likewise useful to psychiatrists who are sometimes called on to examine and treat children. The literature in the field is thoroughly covered and brought up-to-date. For this reason the book is especially useful for anyone who wishes to survey the literature in any aspect of the field. The style of writing is clear and practical, free of most psychiatric jargon, and the indexing is thorough.

H. W. N.

BOOKS RECEIVED

Books received during June are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Advances in Internal Medicine. Volume III. Editors: WILLIAM DOCK, M.D., Long Island College of Medicine, and I. SNAPPER, M.D., The Mount Sinai Hospital. Associate Editors: TINSLEY R. HARRISON, M.D., Southwestern Medical College; CHESTER S. KEEFER, M.D., Evans Memorial and Massachusetts Memorial Hospitals; WARFIELD T. LONGCOPE, M.D.; GEORGE R. MINOT, M.D., Thorndike Memorial Laboratory, and J. MURRAY STEELE, M.D., Goldwater Memorial Hospital, New York University Division. 478 pages; 23.5 × 15.5 cm. 1949. Interscience Publishers, Inc., New York. Price, $8.50.

Advances in Surgery. Volume I. Editorial Board: WILLIAM DEWITT ANDRUS, New York, Chairman; HUGH CAIRNS, Oxford; EDWARD D. CHURCHILL, Boston; CLARENCE CRAFOORD, Stockholm; LESTER R. DRAGSTEDT, Chicago; EMILE HOLMAN, San Francisco; JOHN S. LOCKWOOD, New York; D. W. GORDON MURRAY, Toronto; ALTON OCHSNER, New Orleans, and ISIDOR S. RAVDIN, Philadelphia. 554 pages; 24 × 16 cm. 1949. Interscience Publishers, Inc., New York. Price, $11.00.

Arthritis and Allied Conditions. 4th Edition. By the Late BERNARD I. COMROE, M.D. Completely Revised and Rewritten. Editor: JOSEPH L. HOLLANDER, M.D. Collaborating Editors: NATHAN R. ABRAMS, M.D., VICTOR G. BALBONI, M.D., EDWARD W. BOLAND, M.D., RALPH H. BOOTS, M.D., MORRIS A. BOWIE, M.D., HOWARD C. COGGESHALL, M.D., RICHARD H. FREYBERG, M.D., WALLACE GRAHAM, M.D., W. PAUL HOLBROOK, M.D., JOHN G. KUHNS, M.D., DAVID M. KYDD, M.D., JOHN LANSBURY, M.D., THEODORE A. POTTER, M.D., CHARLES RAGAN, M.D., EDWARD F. ROSENBERG, M.D., and CHARLEY J. SMYTH, M.D. 1108 pages; 24 × 16 cm. 1949. Lea & Febiger, Philadelphia. Price, $16.00.

Cardiovascular Disease: Fundamentals, Differential Diagnosis, Prognosis and Treatment. By LOUIS H. SIGLER, M.D., F.A.C.P., Attending Cardiologist and Chief of Cardiac Clinic, Coney Island Hospital, etc. 551 pages; 23.5 × 15.5 cm. 1949. Grune & Stratton, Inc., New York. Price, $10.00.

Clinical Allergy. 2nd Edition. By LOUIS TUFT, M.D., Assistant Professor of Medicine, Temple University School of Medicine, etc. 690 pages; 24 × 16 cm. 1949. Lea & Febiger, Philadelphia. Price, $12.00.

Conference on Metabolic Aspects of Convalescence. Transactions of the Sixteenth Meeting, New York, N. Y., October 27–28, 1947. Edited by EDWARD C. REIFENSTEIN, JR., M.D., Sloan-Kettering Institute, New York. 168 pages; 23 × 15.5 cm. (paper-bound). 1949. Josiah Macy, Jr. Foundation, New York. Price, $3.00.

Conference on Metabolic Aspects of Convalescence. Transactions of the Seventeenth Meeting, New York, N. Y., March 29–30, 1948. Edited by EDWARD C. REIFENSTEIN, JR., M.D., Sloan-Kettering Institute, New York. 246 pages; 23 × 15.5 cm. (paper-bound). 1949. Josiah Macy, Jr. Foundation, New York. Price, $4.00.

Diagnostic Tests for Infants and Children: Principles, Clinical and Laboratory Procedures, Interpretation. By H. BEHRENDT, M.D. 529 pages; 23.5 × 16 cm. 1949. Interscience Publishers, Inc., New York. Price, $7.50.

The Epitome of Andreas Vesalius. Translated from the Latin with Preface and Introduction by L. R. LIND, Ph.D., University of Kansas; with Anatomical Notes by C. W. ASLING, M.D., Ph.D., University of California, and a Foreword by the Late LOGAN CLENDENING, M.D. 131 pages; 26 × 19.5 cm. 1949. The Macmillan Company, New York. Price, $7.50.

Geriatric Medicine. 2nd Edition. Edited by EDWARD J. STIEGLITZ, M.S., M.D., F.A.C.P., Attending Internist, Suburban Hospital, Bethesda, Maryland (Chairman Staff, 1945–47), etc. 773 pages; 24 × 15.5 cm. 1949. W. B. Saunders Company, Philadelphia. Price, $12.00.

Hematology for Students and Practitioners. Revised 2nd Edition. By WILLIS M. FOWLER, M.D., Professor of Internal Medicine, University of Iowa; with a Chapter by ELMER L. DEGOWIN, M.D., Associate Professor of Internal Medicine, University of Iowa. 535 pages; 24 × 16 cm. 1949. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers. Price, $8.50.

Internal Medicine, being Section VI of Excerpta Medica. Volume II, No. 10, October, 1948. Under the General Editorship of M. W. WOERDEMAN, M.D., F.R.N.A.S., Professor of Anatomy and Embryology in the University of Amsterdam. 159 pages; 25 × 16.5 cm. (paper-bound). October 1948. The Williams & Wilkins Company, Baltimore. Price, By subscription, $37.50.

Manual of Medical Emergencies. By STUART C. CULLEN, M.D., Professor of Surgery; Chairman, Division of Anesthesiology, State University of Iowa College of Medicine, and E. G. GROSS, M.D., Professor and Head of Department of Pharmacology, State University of Iowa College of Medicine. 267 pages; 18.5 × 12.5 cm. 1949. The Year Book Publishers, Inc., Chicago. Price, $3.75.

Medical Etymology: The History and Derivation of Medical Terms for Students of Medicine, Dentistry, and Nursing. By O. H. PERRY PEPPER, M.D., Professor of Medicine, University of Pennsylvania. 263 pages; 24 × 15.5 cm. 1949. W. B. Saunders Company, Philadelphia. Price, $5.50.

Medicine. Volume Two: Diagnosis, Prevention, and Treatment. By A. E. CLARK-KENNEDY, M.D., F.R.C.P., Fellow of Corpus Christi College, Cambridge, etc. 894 pages; 24.5 × 16 cm. 1949. The Williams & Wilkins Company, Baltimore. Price, $7.00.

Oral and Dental Diagnosis, with Suggestions for Treatment. 3d Edition. By KURT H. THOMA, D.M.D., F.D.S.R.C.S.Eng., Professor of Oral Surgery, Emeritus, and Brackett Professor of Oral Pathology, Harvard University, etc. With Contributions by HENRY GOLDMAN, D.M.D., Head of the Dental Department, Beth Israel Hospital, Boston, and FRED TREVOR, D.M.D., Formerly Instructor in Oral Pathology, Harvard Dental School. 563 pages; 24 × 15.5 cm. 1949. W. B. Saunders Company, Philadelphia. Price, $9.50.

Problems of Early Infancy. Transactions of the Second Conference, March 1–2, 1948, New York, New York. With Supplement Covering Special Meetings, July 18–19, 1947, New York, New York. Edited by MILTON J. E. SENN, M.D., Departments of Pediatrics and Psychiatry, Yale University School of Medicine. 120 pages; 23 × 15.5 cm. (paper-bound). 1949. Josiah Macy, Jr. Foundation, New York. Price, $1.00.

Psychosomatic Medicine: The Clinical Application of Psychopathology to General Medical Problems. 2nd Edition. By EDWARD WEISS, M.D., Professor of Clinical Medicine, Temple University Medical School, Philadelphia, and O. SPURGEON ENGLISH, M.D., Professor of Psychiatry, Temple University Medical School, Philadelphia. 803 pages; 24 × 15.5 cm. 1949. W. B. Saunders Company, Philadelphia. Price, $9.50.

Regional Ileitis. By BURRILL B. CROHN, M.D., Consulting Gastroenterologist, Mount Sinai Hospital, New York. 229 pages; 22 × 14.5 cm. 1949. Grune & Stratton, Inc., New York. Price, $5.50.

Rehabilitation of the Tuberculous. 3d Edition. By H. A. PATTISON, M.D., F.A.C.P. 250 pages; 23.5 × 15.5 cm. 1949. The Livingston Press, Livingston, Columbia County, New York. Price, $3.75 postpaid.

Studies of Chronic Pyelonephritis, with Special Reference to the Kidney Function. By FLEMMING RAASCHOU. 260 pages; 25 × 18 cm. (paper-bound). 1948. Ejnar Munksgaard, Copenhagen. Price: Dan.kr. 20,–.

Trends in Medical Education: The New York Academy of Medicine Institute on Medical Education, 1947. Edited by MAHLON ASHFORD, M.D. 320 pages; 21.5 × 14 cm. 1949. The Commonwealth Fund, New York. Price, $3.00.

COLLEGE NEWS NOTES

Proposal of Candidates

The By-Laws of the American College of Physicians require that proposals of candidates for election to Associateship or Fellowship be filed at least 60 days in advance of action by the Credentials Committee. The next meeting of the Committee is scheduled for November 12, and to receive action at that meeting proposals must therefore be filed with the College Headquarters not later than September 12, 1949.

Research Fellowships Applications

Applications are being received to October 1, 1949, for the Research Fellowships in Medicine which the American College of Physicians will make available for the year beginning July, 1950. These Fellowships provide an opportunity for young physicians who are training for academic careers in Internal Medicine or Pediatrics to gain a year of experience in laboratory or clinical investigation. All applications received by October 1 will be reviewed by the Committee on Fellowships and Awards at a meeting to be held on November 12; the Committee will make its recommendations to the Board of Regents the following day, and applicants will be notified shortly thereafter.

The stipends awarded will be in the range of $2,200 to $3,200, depending upon the individual needs of the applicants. Application forms may be obtained from the American College of Physicians, 4200 Pine St., Philadelphia 4, Pa.

Dr. Drenckhahn Appointed Governor for Southern Illinois

In accordance with provisions of the By-Laws, President Fitz has appointed Charles H. Drenckhahn, M.D., F.A.C.P., 602 W. Urbana Ave., Urbana, Ill., to serve as A.C.P. interim Governor for Southern Illinois until the next Annual Business Meeting of the College on April 20, 1950, during the Annual Session in Boston. Dr. Drenckhahn succeeds in this post Dr. Cecil M. Jack, F.A.C.P., Decatur, Ill., who gave devoted service to the College as Governor from 1941 until his untimely death on June 28, 1949.

Dr. Drenckhahn is a graduate of the University of Minnesota Medical School and a Diplomate of the American Board of Internal Medicine. He is a member of the staff of the Carle Memorial Hospital and has been a Fellow of the College since 1939.

1949 A.C.P. Membership Directory

Work on the first complete Directory of the American College of Physicians to be published since 1941 has progressed satisfactorily and is expected to be concluded by the end of September. Copies will be mailed at the earliest possible date to all members and others who have sent their prepublication orders to the College Headquarters. The Directory will be issued in a limited edition only; members who will want but have not yet placed their orders should do so without delay to avoid the possibility of disappointment. The prepublication price, to be billed at time of shipment, is $4.00 a copy to members; $5,00, to non-members and institutions.

Autumn and Winter Regional Meetings of the College

Montana and Wyoming, Great Falls, Mont., September 9, 1949. Dr. Harold W. Gregg, F.A.C.P., Butte, Mont., Governor for the two States, is planning a program

for these meetings which will be attractive not only to local members of the College but to any physician in the area who is especially interested in Internal Medicine. The guest speaker will be Dr. George F. Strong, F.A.C.P., Vancouver, B. C., Can., First Vice President of the College.

North Dakota, Grand Forks, September 10, 1949. The third annual Regional Meeting for North Dakota will be held under the Governorship of Robert B. Radl, M.D., F.A.C.P., Bismarck, and the General Chairmanship of Reinhold O. Goehl, M.D., F.A.C.P., at the Grand Forks Clinic. The program is as follows:

An Approach to the Problem of the Brittle Diabetic.
E. A. HAUNZ, M.D. (Associate), Grand Forks.
Hypoparathyroidism.
ALLAN E. MOE, M.D. (Associate), Fargo.
Early Signs of Neurologic Disease.
G. D. ICENOGLE, M.D. (Associate), Bismarck.
Coronary Disease with Especial Reference to Occurrence in Younger Age Groups.
A. C. GRORUD, M.D. (Associate), Bismarck.
Peptic Ulcer with Especial Reference to Management of Night Pain.
F. T. LYTLE, M.D. (Associate), Fargo.
Splenic Cyst.
C. H. PETERS, M.D. (Associate), Bismarck.
Infectious Mononucleosis.
GEORGE F. STRONG, M.D., F.A.C.P., First Vice President of the College, Vancouver, B. C., Can.
Dicumarol Poisoning.
W. A. STAFNE, M.D., F.A.C.P., Fargo.

There will be a luncheon meeting and a reception and informal dinner, at which Dr. Strong will be the guest speaker.

Oklahoma, Oklahoma City, September 10, 1949. The program for this meeting, to which College members from Arkansas, Kansas and Texas, as well as Oklahoma, will be invited, is being prepared by Wann Langston, M.D., F.A.C.P., Oklahoma City, the local Governor. The guest speaker will be Dr. William S. Middleton, F.A.C.P., Madison, Wis., President-Elect of the American College of Physicians.

Western Pennsylvania, Pittsburgh, September 21, 1949. The very successful series of Regional Meetings for A.C.P. members in Western Pennsylvania held during the Governorship of Dr. Roy R. Snowden, F.A.C.P., Pittsburgh, now Second Vice President of the College, will be continued now under the Governorship of Dr. Charles W. Morton, F.A.C.P., Pittsburgh. It is planned to have an afternoon scientific session at the Woman's Hospital of the Medical Center Group, and a dinner and evening session at the Pittsburgh Athletic Association Annex.

Eastern Canada and New England, Montreal, September 23–24, 1949. A very interesting program is being planned for members in the Maritime Provinces, Newfoundland, Quebec and the New England States by Arthur T. Henderson, M.D., F.A.C.P., Governor for Quebec, and J. S. L. Browne, M.D., F.A.C.P., Chairman of the Program Committee. The meeting will be held at the Windsor Hotel, and will include a day and a half of scientific meetings and a reception and dinner. Dr. Reginald Fitz, F.A.C.P., Boston, A.C.P. President, will be the guest speaker. A large attendance is expected.

Western New York, Buffalo, October 1, 1949. A program of papers in the morning and afternoon and a dinner in the evening is being prepared by Dr. Roy L. Scott, F.A.C.P., Buffalo, General Chairman, and Dr. E. C. Reifenstein, Sr., Syracuse, local Governor. President Reginald Fitz will be the guest speaker.

Puerto Rico, San Juan, October 16, 1949. R. Rodriguez-Molina, M.D., F.A.C.P., Governor, will initiate Regional Meetings in Puerto Rico on this date. The program will be published in a later issue.

Midwest, Indianapolis, November 19, 1949. J. O. Ritchey, M.D., F.A.C.P., Indianapolis, Governor for Indiana, will be Chairman of this meeting, to which College members from Illinois, Indiana, Michigan, Minnesota and Wisconsin will come. The Governors from all these States will coöperate in setting up the program for the 1949 version of one of the largest of the College's Regional Meetings.

New Jersey, Newark, November 30, 1949. Under the Governorship of Dr. George H. Lathrope, F.A.C.P., Newark, and with Dr. J. F. Pessel, F.A.C.P., Trenton, as Chairman of the Program Committee, arrangements are progressing satisfactorily for another of the fine New Jersey Regional Meetings. It is expected that President Reginald Fitz, F.A.C.P., Boston, Secretary-General George Morris Piersol, M.A.C.P., Philadelphia, Regent Edward L. Bortz, F.A.C.P., Philadelphia, and Treasurer William D. Stroud, F.A.C.P., Philadelphia, will be among the guest speakers.

Southeastern States, Birmingham, Ala., December 10, 1949. This meeting will be held at The Medical College of Alabama and the Thomas Jefferson Hotel, with arrangements by Dr. E. Dice Lineberry, F.A.C.P., Birmingham, local Governor, Dr. Edgar G. Givhan, Jr., F.A.C.P., Birmingham, General Chairman, and Dr. Duward O. Wright, F.A.C.P., Birmingham, Chairman of the Arrangements Committee. This Regional Meeting will be a part of and will conclude the A.C.P. Postgraduate Course on Blood Dyscrasias, to be given at The Medical College of Alabama by James B. McLester, M.D., F.A.C.P., Director, December 6–10, 1949.

Kansas, Topeka, March 17, 1950. Dr. William C. Menninger, F.A.C.P., Topeka, Governor for Kansas, will prepare the program. Dr. Hugh J. Morgan, F.A.C.P., Nashville, Tenn., Regent and Past-President of the College, has agreed to attend as guest speaker.

Other Meetings. The Arizona and Virginia sections of the American College of Physicians plan to hold their Regional Meetings in the late winter or early spring of 1950, but have not as yet selected definite dates.

Additional Life Members

Grateful acknowledgment is made to the following Fellows of the College for their recent subscriptions to Life Membership:

W. E. Bayley, La Fayette, Ind.
Joseph Augustine Lundy, Worcester, Mass.
Terence Lloyd Tyson, New York, N. Y.
Joseph Edward Walther, Indianapolis, Ind.

A.M.A. Distinguished Service Medal

The American College of Physicians takes pride in the recent award of the Distinguished Service Medal of the American Medical Association to one of its outstanding Fellows, Seale Harris, M.D., Birmingham, Ala.

Myron M. Weaver, Assistant Dean of Medical Sciences and Associate Professor of Medicine and Public Health, University of Minnesota, has accepted the Deanship of the new Faculty of Medicine of the University of British Columbia and assumed that position at Vancouver on July 1. It is hoped that plans for the development of the new medical school will be presented from time to time in this publication for the many readers who will be interested in them.

Harry M. Hedge, M.D., F.A.C.P., Chicago, has been designated as President-Elect of the Illinois State Medical Society.

Henry Packer, M.D., F.A.C.P., Memphis, succeeded Dr. Frank L. Roberts, F.A.C.P., as Professor of Preventive Medicine and Public Health and Head of the Department in the University of Tennessee College of Medicine, on July 1. Dr. Roberts has assumed the Assistant Deanship of the College.

Joseph C. Placak, M.D., F.A.C.P., Cleveland, and Louis Mark, M.D., F.A.C.P., Columbus, have been selected as President and President-Elect, respectively, of the American College of Chest Physicians.

It has recently been announced that the Long Island College of Medicine and the Syracuse University College of Medicine will become parts of the State University of New York shortly and will thereafter become enlarged as the Brooklyn metropolitan and up-state medical centers under the program for which $5,000,000 or more was appropriated by the 1949 Legislature. It is hoped that developments in the building of these medical centers can be presented in later issues.

Euclid M. Smith, M.D., F.A.C.P., Hot Springs National Park, has been elected President of the Arkansas Medical Society.

Ward Darley, M.D., F.A.C.P., Denver, A.C.P. Governor for Colorado, has been appointed Vice President and Dean, Department of Medicine, of the University of Colorado.

Drs. George H. Garrison, F.A.C.P., and Lewis J. Moorman, F.A.C.P., Oklahoma City, have been elected as President and Treasurer, respectively, of the Oklahoma State Medical Association.

Rear Admiral, Clifford Swanson, M.D., F.A.C.P., Surgeon General of the Navy and *ex officio* A.C.P. Governor, has been awarded an honorary Doctor of Laws degree by Northern Michigan College of Education, Marquette, Mich.

Otis L. Anderson, M.D., F.A.C.P., has been inducted into office as an Assistant Surgeon General of the U. S. Public Health Service.

Louis H. Sigler, M.D., F.A.C.P., Brooklyn, New York, has presented to the College Library of Publications by Members, a copy of his book, "Cardiovascular Disease, Fundamentals, Differential Diagnosis, Prognosis and Treatment," newly published by Grune & Stratton, New York, N. Y.

Friends of the Jefferson Medical College and Hospital of Philadelphia and of the Germantown Dispensary and Hospital will be interested to learn that the two institutions have reached an agreement to coöperate in their major efforts. While the two institutions in no sense will be merged, the College will be able to use the hospital's facilities for the training of medical students and the hospital will have the benefits of the aid and direct interest of the Jefferson Faculty.

Election of Officers, American Medical Association

At the recent annual session of the American Medical Association, held in Atlantic City, N. J., in June, Dr. Ernest E. Irons, F.A.C.P., Chicago, was installed as President for 1949–1950. Dr. Elmer L. Henderson of Louisville, Ky., was elected President-Elect to succeed Dr. Irons. Dr. James Francis Norton, Jersey City, N. J., was elected Vice President. Dr. George F. Lull, F.A.C.P., and Dr. Josiah J. Moore, F.A.C.P., both of Chicago, were re-elected as Secretary and Treasurer, respectively. Francis F. Borzell, M.D., F.A.C.P., Philadelphia, was elected to succeed himself as Speaker of the House of Delegates, and James R. Reuling, M.D., F.A.C.P., Bayside, N. Y., was elected as Vice Speaker. Louis H. Bauer, M.D., F.A.C.P., Hempstead, N. Y., was re-elected as a Trustee and Thomas P. Murdock, M.D., F.A.C.P., Meriden, Conn., was elected a member of the Judicial Council.

Chicago was selected as the site of the 1952 annual session.

The following Fellows of the College were elected on June 28 by the Section on Internal Medicine: Arthur Bloomfield, San Francisco, Chairman; Ralph A. Kinsella, St. Louis, Vice Chairman; Walter L. Palmer, Chicago, Secretary; Charles T. Stone, Galveston, Representative to the House of Delegates; William D. Stroud, Philadelphia, Alternate; Cecil J. Watson, Minneapolis, M. A. Blankenhorn, Cincinnati, and Arthur Bloomfield, San Francisco, to the Executive Committee.

Separate Medical Service for the U. S. Air Force

As of July 1, 1949, a separate medical service has been authorized for the U. S. Air Force. Major General Malcolm C. Grow has been designated as the Surgeon General and given an organizational and functional position directly under the Chief of Staff of the Air Force. It has been planned that physicians in the Air Force will have opportunity to gain advanced training in clinical medicine and in the investigation of problems important to aviation medicine. It is anticipated that the majority of the Army medical officers now serving with the Air Force will be transferred to the Air Force by the end of July, but it is possible that for some longer period some Army personnel will continue to be on duty with the Air Force without being commissioned therein.

National Heart Institute Grants

National Heart Institute grants of more than $1,200,000 to support heart disease research work in medical schools and hospitals in twenty-one states, the District of Columbia and Canada have been announced by the Federal Security Administrator recently. The grants were approved by Surgeon General Leonard A. Scheele, F.A.C.P., of the Public Health Service, following recommendation by the National Advisory Heart Council.

Dr. C. J. Van Slyke, Director of the National Heart Institute, states that only a portion of the federal funds to be awarded for heart disease research during the current fiscal year is represented in the above. Additional grants for new heart research and for construction of heart research facilities and laboratories are expected to be announced shortly.

Established last August (1948) under authority of the National Heart Act, the National Heart Institute is one of the National Institutes of Health, the research arm of the Public Health Service, with headquarters in Bethesda, Md. In addition to conducting scientific research in its own laboratories, the Institute administers federal funds supporting research and training related to the cause, prevention, and methods of diagnosis and treatment of heart disease in outside institutions throughout the country.

American College of Surgeons Clinical Congress and 6th Inter-American Congress of Surgery

The 35th Clinical Congress of the American College of Surgeons and the 6th Inter-American Congress of Surgery will be held in Chicago, October 17–23, 1949. Sir James R. Learmonth, of Edinburgh, will deliver the fourth Martin Memorial Lecture. Dr. Dallas B. Phemister, of Chicago, President of the College, will be succeeded by Dr. Frederick A. Coller, of Ann Arbor, Mich., now President-Elect. Lord Webb-Johnson, of London, President of the Royal College of Surgeons of England, will deliver the Fellowship Address at the Convocation. Television of operations in color from St. Luke's Hospital to the Stevens Hotel, which is headquarters, will be a feature of each day's program.

The National Society for Medical Research

The Board of Regents recently approved membership of the American College of Physicians in the National Society for Medical Research, a society limited by its charter to performing an informational function in legislative matters which is doing everything it can properly do to present purely factual information to the public.

Critical legislation is now before both the Senate and House of Representatives which would affect animal experimentation (a) in the District of Columbia, (b) in governmental laboratories, (c) in research and teaching programs financed by government grants. Both antivivisection measures and, on the other hand, positive legislation to facilitate animal research are up for consideration. The outcome of this contest is of tremendous importance both for its direct effect and for the precedents it will establish. Dr. A. J. Carlson, F.A.C.P., of the National Society for Medical Research, makes the following points:

1. "Use whatever contacts are at your disposal to make sure that your Senators and Representatives know what is involved in the pending bills. Friends of medical research must write more.

2. "Give whatever aid you can—money, materials, personal service or advice—to the Washington Committee for Health and Research, which is carrying on the actual legislative battle in behalf of animal experimentation.

3. "Let your staff, students, members and customers know about this legislative crisis."

Society of Neurology and Psychiatry of Hawaii Organized

A group of physicians in Honolulu have organized the Society of Neurology and Psychiatry of Hawaii. The constitution was formally adopted on April 13, 1949. The Officers are R. D. Kepner, M.D., F.A.C.P., President; Thomas S. Bennett, M.D., Vice President; and H. Joseph Simon, M.D., Secretary-Treasurer.

OBITUARIES

DR. GEORGE L. COOK

The death of Dr. George Lindsay Cook on March 8, 1949, brought a deep sense of loss to a host of friends and patients throughout Florida. Dr. Cook had practiced in Tampa since 1925, and held great influence in medical affairs in his community. His courtesy, unfailing kindness and sympathy endeared him to a host of friends.

He was born in Augusta County, Va., on October 10, 1886. He took his academic training at the University of Virginia, and graduated in medicine from the Medical College of Virginia in 1913. He interned at the Gouverneur and Woman's Hospitals in New York between 1914 and 1916. From 1917 to 1919, he served as a Captain in the Medical Reserve Corps of the U. S. Army. After completing his military service, he spent two years at the Bellevue and Willard Parker Hospitals in New York City. He entered the practice of pediatrics in Atlanta, Ga., in 1921, and moved to Tampa in 1925.

Dr. Cook was attending pediatrician to the Tampa Municipal and St. Joseph's Hospitals, and was a member of the American Academy of Pediatrics. He became a Fellow of the American College of Physicians in 1929 and a Diplomate of the American Board of Pediatrics in 1934.

Dr. Cook died of a coronary occlusion after having suffered a previous attack three years before. Although realizing the danger, he steadfastly refused to curtail his work during the period of medical emergency. His loss will be deeply felt.

WILLIAM C. BLAKE, M.D., F.A.C.P.,
Governor for Florida

DR. SAMUEL ELGART

Dr Samuel Elgart, born in Providence, R. I., September 20, 1911, died in Cincinnati, Ohio, on June 18, 1949.

Dr. Elgart received his B.S. degree from Tufts College in 1934 and his M.D. degree from Tufts College Medical School in 1938. His internship was served at Beth Israel Hospital, Boston, 1938–39, and he continued his postgraduate training in medicine and biochemistry at Duke University the following year. For two years, 1940–42, he was associated with the May Institute of Medical Research and the University of Cincinnati College of Medicine, in biochemistry. Since 1943 he had been on the Staff of the Cincinnati General and Jewish Hospitals and had attended the Beckman Dispensary, the Hamilton County Home and Chronic Disease Hospital. Since 1944 he had been an Instructor in Medicine at the University of Cincinnati College of Medicine.

Dr. Elgart was always interested in clinical investigation and spent the major part of his active medical years in the study of endocrinologic problems, more recently utilizing radioactive isotope technics. He received great personal satisfaction in his teaching opportunities, whether they represented the teaching of under-graduate medical students, participation in postgraduate medical courses, or the teaching of student nurses. His teaching and investigative career has been unfortunately prematurely ended, and his many friends and professional associates feel that medicine has sustained a very real loss in his passing.

Dr. Elgart was elected an Associate of the American College of Physicians in April, 1938. He was a Diplomate of the American Board of Internal Medicine and was active in the American Diabetes Association together with other local and national medical societies.

CHARLES A. DOAN, M.D., F.A.C.P.,
Governor for Ohio

DR. CLIFFORD P. RUTLEDGE

Dr. Clifford Phillip Rutledge, of Shreveport, La., Director of the Department of Radiology of the Highland Clinic and Highland Sanitarium, and Fellow of the American College of Physicians since 1930, died on January 31, 1949, at the age of 63.

A native of Lee County, Ala., Dr. Rutledge obtained B.S. and Ph.G. degrees from Alabama Polytechnic Institute in 1903, and practiced pharmacy for some years thereafter. He entered the School of Medicine of the University of Alabama in 1908 and graduated in 1912. Shortly after graduation he entered practice in Shreveport.

In 1917 he volunteered for service in the U. S. Army, and was discharged with the rank of Captain in 1919.

Following his discharge he took up the specialty of radiology, and upon formation of the Highland Clinic was named Director of its Department of Radiology, a position which he held until the time of his death.

Dr. Rutledge was a Diplomate of the American Board of Radiology, and a member of the Shreveport Fourth District, Louisiana State and Tri-State Medical Societies, the Southern and American Medical Associations, the Radiological Society of North America, the American Roentgen Ray Society, and the American College of Radiology. He had held office as President of the Louisiana Radiological and Shreveport Medical Societies.

Dr. Rutledge was recognized as one of the leading radiologists in the State and was active in religious affairs in the city of Shreveport.

EDGAR HULL, M.D., F.A.C.P.,
Governor for Louisiana

DR. JOSEPH ENOCH GICHNER

Joseph Enoch Gichner, M.D., of Baltimore, Md., died on March 8, 1949, at the age of 85. An Associate of the American College of Physicians since 1924 by virtue of membership in the old American Congress on Internal Medicine, Dr. Gichner was a graduate of the University of Maryland School of Medicine, 1890, and was Emeritus Professor of Clinical Medicine and Physical Therapeutics in that Faculty.

DR. FREDERIC W. HALL

Dr. Frederic Wilhelm Hall, son of Frank Johnson Hall, eminent pathologist of Kansas City, Mo., died May 21, 1949.

Dr. Hall was born June 5, 1911. He attended Fresno State College, Fresno, Calif., and graduated in 1936 from the University of Kansas School of Medicine. He served a residency at the Hertzler Clinic, Halstead, Kans. and was associated for nine years with the Snyder-Jones Clinic in Winfield, Kans. He opened an office in Ponca City, Okla., in the Fall of 1949. He had served in World War II from April, 1941, to September, 1945, and held the rank of Major in the Medical Corps of the Army of the United States.

Dr. Hall was elected to Associateship in the American College of Physicians in 1942. He became a Diplomate of the American Board of Internal Medicine in 1948.

Dr. Hall's sudden and entirely unexpected death cut short a promising career in internal medicine and in his chosen field of gastro-enterology.

HAROLD H. JONES, M.D., F.A.C.P.

ABRIDGED MINUTES OF THE BOARD OF REGENTS

NEW YORK, N. Y.

APRIL 1, 1949

The third meeting of the Board of Regents during the 30th Annual Session, and the first meeting of the new Board of Regents, was held at the Waldorf-Astoria Hotel, New York, N. Y., Friday, April 1, 1949, convening at 1:40 p.m., with President Reginald Fitz presiding and with Mr. E. R. Loveland acting as Secretary. The following were present:

Reginald Fitz, *President;* George F. Strong, *First Vice President;* Roy R. Snowden, *Second Vice President;* Turner Z. Cason, *Third Vice President;* David P. Barr, A. B. Brower, Alex. M. Burgess, Ernest H. Falconer, Cyrus C. Sturgis, Walter B. Martin, LeRoy H. Sloan, Harold H. Jones, T. Grier Miller, Charles F. Moffatt, and Charles A. Doan, *Vice Chairman, Board of Governors.*

The Secretary read an abstract of the Minutes of the preceding meeting of the Board of Regents, which were accepted as read.

President Fitz introduced Dr. Fay A. LeFevre, Vice President and Chairman of the Executive Committee of the Academy of Medicine of Cleveland, Dr. Vernon C. Rowland, F.A.C.P., of Cleveland, and Mr. Edward Brennan, of the Cleveland Convention and Visitors' Bureau. Each of them extended an invitation to the College to hold its 1951 Annual Session in Cleveland, and they presented such information as desired about the facilities available. They were all cordially thanked for their invitation, and were told that the Board would take the Cleveland invitation up with other invitations to be considered later in the meeting.

In accordance with the chief purposes of this meeting of the Board of Regents, the President proceeded with the organization of the Board and its Committees for the succeeding year.

Dr. Walter B. Martin nominated Dr. George Morris Piersol for re-election as the Secretary-General; he was seconded by Dr. A. B. Brower, and was unanimously re-elected.

Dr. T. Grier Miller moved the re-election of Dr. William D. Stroud as Treasurer. The nomination was seconded, and Dr. Stroud was unanimously so re-elected.

Dr. Chester S. Keefer was nominated and seconded as the General Chairman of the Boston Annual Session, 1950, and his election was unanimously confirmed.

In accordance with regulations of the By-Laws and/or the Minutes of the Board of Regents, committees for 1949–1950 were elected or appointed. (Inasmuch as the personnel of these committees have previously been published in this journal, this portion of the proceedings is omitted.)

Dr. Charles A. Doan, as Vice Chairman of the Board of Governors, in the absence of the Chairman, Dr. Walter L. Palmer, reported for that Board. He requested some consideration of some kind of limitation of the attendance at the Annual Sessions of the College, so that members would have access to and seats in the main auditorium and other scheduled programs. Accordingly, the Board of Governors had adopted a resolution suggesting to the Board of Regents as an experiment at the next Annual Session that attendance be limited to Masters, Fellows and Associates and guests specifically invited and sponsored by these members. The Board of Governors felt the sessions were becoming so large that meeting facilities are inadequate, and some effort must be made to hold the attendance down to the available facilities. The suggestion was that guests that are sponsored by members shall notify the Executive Office in advance. It had been disclosed at the New York Session that more than half of the guests came unsponsored.

Dr. Doan discussed the question as to whether the College should have an educational program as broadly available to doctors in general as possible, or whether its first obligation should not be directed to its formal members, and that the remaining facilities be made available to guests who shall be sponsored by members. The College had already attempted to set aside a block of seats for its members, but there was no effective manner in which this could be enforced. Therefore, the Governors' recommendation was made as a suggestion for an experiment for 1950.

All angles of the matter were generally discussed by members of the Board of Regents. A motion was made by Dr. Walter B. Martin, seconded by Dr. Alex. M. Burgess, that the recommendation of the Governors be approved.

There was much discussion of the motion, many wishing to extend the benefits of the annual meetings of the College to the largest possible number of interested physicians. It was appreciated by all that the facilities to accommodate guests vary from year to year, according to the cities where the Annual Sessions are held. There developed a feeling that the President, General Chairman, local Committees and the Executive Secretary should carefully survey the facilities that will be available in Boston, and be prepared to report at the next meeting of the Board of Regents. Accordingly, it was moved by Dr. Cyrus C. Sturgis and seconded by Dr. A. B. Brower that the previous resolution be temporarily tabled until the next meeting of the Board of Regents, and this resolution was unanimously adopted.

On motion by Dr. George F. Strong, seconded and regularly carried, the President, General Chairman and the Executive Secretary were authorized to complete all necessary arrangements for the 1950 Annual Session.

The meeting was now opened to a discussion of the meeting city for the 1951 Annual Session of the College. Complete invitations had been received from St. Louis and Cleveland. Possibly for some later year, the Board was asked by Dr. George F. Strong to consider the possibilities of Toronto. Dr. Cyrus C. Sturgis bespoke the opportunity of Detroit again entertaining the College. The discussion, however, narrowed down to the invitations from St. Louis and Cleveland, the first being sponsored primarily by Dr. Ralph A. Kinsella, F.A.C.P., College Governor for Missouri, and the latter being supported by Dr. Fay A. LeFevre, F.A.C.P., and Dr. Vernon C. Rowland, F.A.C.P., of Cleveland. It was pointed out that each city has fine meeting facilities; each city had guaranteed an adequate number of hotel rooms; each city had been supported in its invitation by its local medical groups, the Academy of Medicine, the County Medical Society, etc.; in each instance the cost to the College for rental of meeting space was comparable, approximately $3,000.00. The discussion carried into the matter of the location of the cities. It has been a longer period since the College met in St. Louis than in Cleveland. Furthermore, two successive annual meetings had been scheduled on the eastern seaboard (New York, 1949, and Boston, 1950). There appeared an obligation to consider the far western members in 1951, by taking the meeting farther west than Cleveland. The available dates for the Annual Session in St. Louis and Cleveland were equally satisfactory—April 9–13 in St. Louis; April 16–20 in Cleveland.

A motion was made and seconded to accept the St. Louis invitation.

The motion was further discussed by Dr. David P. Barr, formerly of St. Louis, who pointed out both the strong and weak points of St. Louis. Dr. Ernest H. Falconer expressed the opinion that it had not been too good policy to plan two successive meetins on the eastern seaboard, and said that many of the far western men would favor St. Louis.

The motion was put to vote, and St. Louis was unanimously selected; the dates, April 9–13, 1951.

At this point, President Fitz brought up the matter that the Army some time ago had sent a communication to deans of medical schools, asking them to encourage staff members to go abroad and serve in the capacities of consultants, in order to

help Army training programs, but results had thus far not proved very satisfactory. He said a group of younger men in New York were now preparing a proposal, copy of which he distributed, but it had nothing to do officially with the College. These gentlemen wished to bring this up through us to the attention of teaching staffs in medical schools, with the hope that more progress can be made toward making the Army more worth while educationally. He said that they hoped that if the deans and heads of departments realize that the younger men themselves were really concerned about this, there might be some impetus to the promotion of the program.

Dr. Walter B. Martin stated that there is a great shortage of trained men in the Army hospitals in the occupied zones, and that in some of the small hospitals there is no one between a commanding officer and an interne—often no trained surgeon, not even a trained interne, not a single ophthalmologist and possibly one trained orthopedist on duty. Anything that could be done to remedy that condition would certainly be well worth while, he thought.

Dr. George F. Strong referred to the acute conditions in Australia, where their isolation is possibly greater than ever before. He said they are almost entirely cut off from America and Canada. The dollar situation is such that they cannot even subscribe to medical journals from this Continent. He raised the question as to whether the American College of Physicians could not sponsor visiting professorships by which two or three men might visit Australia annually, or semi-annually, as a gesture of friendship and coöperation. Dr. Strong suggested the matter be given consideration and possibly referred to some appropriate committee for study.

Dr. Cyrus C. Sturgis suggested the possibility of interesting the Kellogg Foundation in one or two fellowships for Australian and New Zealand men. He said the Foundation is interested in extending its fellowships to Canada, but could not express an opinion as to their interest in extending them to Australia.

Dr. Strong clarified his proposal by saying that he was not thinking especially of bringing their men here, but of sending a group of competent men on a post-graduate tour of Australia.

On motion by Dr. George F. Strong, seconded by Dr. Walter B. Martin, and carried, it was

RESOLVED, that the Committee on Fellowships and Awards make a survey of the possibilities, both with respect to bringing people to America from Australia and of sending teachers to Australia, and to report back at the next meeting of this Board.

There being no further business, the meeting *adjourned* at 2:20 o'clock.

Attest: E. R. LOVELAND,
Secretary

. . . President Fitz, following the meeting and in accordance with earlier directions of the Board of Regents concerning representation on the Advisory Council on Medical Education, appointed Dr. Marion A. Blankenhorn, Cincinnati, Ohio, as the College representative. . . .

ABRIDGED MINUTES OF THE BOARD OF GOVERNORS

NEW YORK, N. Y.

MARCH 30, 1949

A regular meeting of the Board of Governors, during the 30th Annual Session, convened at one o'clock, March 30, 1949, at the Waldorf-Astoria Hotel, New York, N. Y., with Dr. Walter L. Palmer, Chairman of the Board, presiding and with Mr. E. R. Loveland acting as Secretary. The following were in attendance:

Governors:

Leland P. Hawkins, Los Angeles	California (Southern)
*Louis S. Faust, Denver	Colorado
Thomas P. Murdock, Meriden	Connecticut
Wallace M. Yater, Washington	District of Columbia
Cecil M. Jack, Decatur	Illinois (Southern)
Robert M. Moore, Indianapolis	Indiana
Harold H. Jones, Winfield	Kansas
Chester S. Keefer, Boston	Massachusetts
Joseph D. McCarthy, Omaha	Nebraska
Edward C. Reifenstein, Sr., Syracuse	New York (Western)
*Bert F. Keltz, Oklahoma City	Oklahoma
Edward L. Bortz (Vice Chairman), Philadelphia	Pennsylvania (Eastern)
R. R. Snowden, Pittsburgh	Pennsylvania (Western)
John L. Calene, Aberdeen	South Dakota
William C. Chaney, Memphis	Tennessee
Louis E. Viko, Salt Lake City	Utah
Herbert K. Detweiler, Toronto	Ontario
*Elmer R. Smith, Ancon	Republic of Panama and the Canal Zone
Arless A. Blair, Fort Smith	Arkansas
*Ernest H. Falconer, San Francisco	California (Northern)
Benjamin F. Wolverton, Cedar Rapids	Iowa
Edgar Hull, New Orleans	Louisiana
Douglas Donald, Detroit	Michigan
*Harry L. Smith, Rochester	Minnesota
Ralph A. Kinsella, St. Louis	Missouri
Harry T. French, Hanover	New Hampshire
George H. Lathrope, Newark	New Jersey
Paul F. Whitaker, Kinston	North Carolina
Robert B. Radl, Bismarck	North Dakota
Herman A. Lawson, Providence	Rhode Island
Robert Wilson, Jr., Charleston	South Carolina
Ellsworth L. Amidon, Burlington	Vermont
George H. Anderson, Spokane	Washington
Delivan A. MacGregor, Wheeling	West Virginia
*Hugh A. Farris, St. John	Maritime Provinces
Arthur T. Henderson, Montreal	Quebec
Jose J. Centurion, Havana	Cuba
E. Dice Lineberry, Birmingham	Alabama
Leslie R. Kober, Phoenix	Arizona
Lemuel C. McGee, Wilmington	Delaware
William C. Blake, Tampa	Florida
Carter Smith, Atlanta	Georgia
Samuel M. Poindexter, Boise	Idaho
Walter L. Palmer (Chairman), Chicago	Illinois (Northern)
J. Murray Kinsman, Louisville	Kentucky
Richard S. Hawkes, Portland	Maine
Wetherbee Fort, Baltimore	Maryland
*Wesley Lake, Greenville	Mississippi
Harold W. Gregg, Butte	Montana and Wyoming

* Alternate.

Asa L. Lincoln, New York	New York (Eastern)
Charles A. Doan, Columbus	Ohio
Howard P. Lewis, Portland	Oregon
David W. Carter, Jr., Dallas	Texas
Karver L. Puestow, Madison	Wisconsin
John W. Scott, Edmonton	Alberta and British Columbia
Charles H. A. Walton, Winnipeg	Manitoba and Saskatchewan
*James O. Gillespie	United States Army
Paul B. Magnuson	United States Veterans Administration

Guest:

Walter W. Palmer ..... President

By resolution regularly carried, the Minutes of the preceding meeting were merely abstracted by the Secretary.

Chairman Walter L. Palmer introduced President Walter W. Palmer, who responded with a few remarks.

The Chairman then proceeded with the election of a Vice Chairman to succeed Dr. Edward L. Bortz, whose term as Governor had expired.

. . . Two candidates were nominated as Vice Chairman; written ballots were cast; and Dr. Charles A. Doan, Governor for Ohio, was declared elected. . . .

Chairman Palmer then proceeded to the election of a representative from the Board of Governors to fill the vacancy on the Committee on Credentials, to succeed Dr. Wallace M. Yater, whose term expired.

Dr. William C. Chaney nominated Dr. J. Murray Kinsman from Kentucky. Dr. Wallace M. Yater moved that the nominations be closed. The motion was seconded by Dr. Edgar Hull, voted upon and carried, and the Secretary was instructed to cast one ballot for the election of Dr. Kinsman.

Chairman Palmer then called for the appointment of a member on the Advisory Committee on Postgraduate Courses to succeed Dr. Edward L. Bortz, who was retiring from the Board of Governors.

(Chairman Palmer obtained permission to delay his appointment until after the elections at the Annual Business Meeting on Thursday, March 31. Subsequently he appointed Dr. Thomas M. McMillan, of Philadelphia, newly elected Governor for Eastern Pennsylvania, to succeed Dr. Bortz not only as a member of the Committee, but as Chairman.)

Chairman Palmer then opened the meeting for general discussions of problems of the College, and asked the Secretary, Mr. E. R. Loveland, to introduce the subject of Regional Meetings.

Mr. Loveland pointed out that often the dates of Regional Meetings either conflict or are so close together that it makes it difficult to arrange for the President, President-Elect, or Officers, to accept speaking engagement for the Regional Dinner-Meeting, and Regents in those instances must be called upon. He asked the Governors to keep him advised longer in advance, if possible, concerning the dates of their meetings and their requirements. He restated that the Central Office is prepared to print and distribute all Regional Meeting programs, to furnish a speaker for the dinner-meeting and to help in such other respects as Governors desire.

Chairman Palmer then asked for a discussion of the whole subject of the rôle of the Governor in endorsing candidates for membership in the College, and asked Dr. Wallace M. Yater, the retiring member of the Credentials Committee, to introduce the discussion.

Dr. Yater said that from his experience and observation, he felt it takes too long for a new Governor to know what his duties are and all the details connected

* Alternate.

therewith. He proposed that there be established an indoctrination of the new Governors each year—a period set aside for the specific instruction and aid of the new Governors—a meeting at which the Chairman of the Credentials Committee, the Secretary-General and the Executive Secretary might go over in detail the responsibilities of the Governors and make suggestions for the most expeditious manner of carrying them out. Dr. Yater moved that such a program be initiated, and it was seconded by Dr. Richard S. Hawkes.

In the discussion it was brought out that the Executive Secretary and the Credentials Committee, working together, shall be instructed to carry out these arrangements. The motion was thereafter voted upon and carried.

Chairman Palmer then asked for a general discussion among the Governors of problems relating to the admission of candidates.

Dr. George H. Lathrope (Governor for New Jersey): Mr. Chairman, I would like again to lay before this group a thought, perhaps not for action today, in regard to the age at which men are admitted to the College. We have to get in our minds pretty clearly two things—first, what the diploma of the American Board of Internal Medicine means, and, second, what Fellowship in the College means.

As I take it, the diploma of the American Board, as they hand it to a man, says to him, "You are qualified; you have attained qualifications necessary to make you an Internist." It doesn't say anything about how good an Internist he is; how much experience he has had, and a few things of that kind. What the College says to a man when it gives him a Fellowship Certificate, or, more important, what it says to the public when his Fellowship Certificate is placed on the wall, "Here is a qualified, experienced Internist; a man who has matured in his medical work to such a point that the American College of Physicians is willing to recommend him to the public-at-large."

Now those are two different things. The American Board diploma is related to the M.D. degree, just as a Master's degree is related to a Bachelor's degree that may come along in a year or two after a man has obtained his B.A. The Ph.D. is another thing—there is a wider separation and harder work there. Now, it is the same thing with a Fellowship in the College. Fellowship in the College should mean maturity in experience, and I do not think it quite means that just now.

There is a growing tendency—a very good one—we see it in the Credentials Committee, and you all see it; we all see it as Governors—for the young men as soon as they get out of medical school and the hospital, and can establish themselves in their preliminary training for the American Board, to take the Board examinations as fast as they can. That is the time for them to do it, when they are keen and fresh. The implication has been widespread in the last few years that as soon as a man has passed his American Board, that that is an open sesame to the College, and the two things have followed each other rather rapidly in a good many cases. Thus a man may become a Fellow, having gone through all the stages, as early as thirty. I think that is a little too soon. Perhaps there are not many, but there are some. There is a much larger proportion that reach the College in the next five years. To my mind they are a little lacking in experience and in the maturity process. I should like to see a definite age limit of thirty-two years for Associateship put in the rules or in the By-Laws. I just want to suggest this for the Board to think over, because I think it is important.

Dr. Thomas P. Murdock (Governor for Connecticut): Mr. Chairman, that seems to be our chief problem in Connecticut. We have seen both situations—the return of a proposal by the Credentials Committee, telling the sponsors that the candidate is too young and too recently out of medical school; also the opposite, in which the Credentials Committee has stated that probably the candidate is too old. We also have had candidates deferred because they have reportedly not produced anything, have not done any writing. I agree heartily with Dr. Lathrope, that probably

the time has come to put an age limit on candidates. When one figures that a young man is out of his residency probably at the age of thirty-one and is eligible for his Board examination at thirty-three, he moves on to a Fellowship in the College at thirty-six to thirty-eight. I think, however, that that is a good age period for these young men.

Dr. Paul F. Whitaker (Governor for North Carolina): Mr. Chairman, I would like to speak in support of Dr. Lathrope's suggestion. In North Carolina we have three teaching institutions. Often a young man who is doing research work or pursuing further training writes to me to determine the policy of the College in regard to admission. It is our custom to inform him that the candidate should complete his training and be established in a permanent location. I agree with Dr. Lathrope that many men feel that because they have been certified by the American Board of Internal Medicine they have automatically become eligible for Fellowship in the College. I know of no other organization that commands more respect in our part of the country than does the College, and I feel that putting an age limit of thirty or thirty-one for Associateship would be a wise policy and would strengthen the College.

Chairman Palmer then asked Dr. Lathrope to discuss the matter of permanent location as a prerequisite for Associateship.

Dr. Lathrope: We feel that is important. The candidate should be located in practice or some type of work sufficiently long to be known by our Fellows in his community, so that there are local men to sponsor him and local men to support his candidacy. The Credentials Committee wants to know what kind of medicine he is practicing, whether he is ethical, what sort of a citizen he is. We think he should be established for two years in one place.

While I am speaking, may I say a word in response to Dr. Murdock about older candidates? The older men, around fifty to sixty years of age, who have been handed back by the Committee are usually men who have not as yet passed their Board examinations, and the Committee feels that after forty-five it is pretty difficult for them to do so, although some men do. Therefore, the Committee does not wish to admit to Associateship any candidate until he has a reasonable opportunity and expectancy to qualify for Fellowship three to five years hence.

Dr. Leland P. Hawkins (Governor for Southern California): Would it be possible, in the next communication that goes to the membership, for the Credentials Committee to put in an announcement with that information included to each member, reiterating what the qualifications are for Associateship and for Fellowship, so that we, as Governors, will not get proposals of candidates who really are not ready for membership? Once these proposals reach us—and they oftentimes come on the basis of friendship—the Governors may be embarrassed to refuse endorsement. I think the Fellows-at-large need some education concerning the requirements.

Dr. Lathrope: Mr. Chairman, as you all know from the discussion at our previous meeting, the Executive Secretary and the Chairman of the Committee on Credentials are going to prepare a specific, suggestive outline of the requirements that an Associate must fulfill to become a Fellow. I believe that this communication should include something about the requirements for Associateship too—that the candidate should have already attained eligibility for admission to his Board examinations and that he should have been established at least a year and one-half, or two years, in one place for practice, so that the men in his surrounding area shall know what sort of work he does and what sort of a man he is. Endorsing candidates is a responsibility of the Governors entirely. They are not under obligation to endorse any candidate who is not qualified, and they should be perfectly free to return proposals to the sponsors, with an explanation of why the candidate is not eligible.

Dr. Wallace M. Yater: Mr. Chairman, there is another reason for requiring two years of residency in the community. At the end of that two years, the young

man is then eligible to take his Board, which gives him a whole five years in which to attain certification, so that if he fails twice, he still has a third chance at it and will have an opportunity to complete his Board examinations by the end of his five-year Associate term. There is one modification I want to make to Dr. Lathrope's statement about these suggestions that are to be sent to the Governors. These regulations are to be sent also to every newly elected Associate, so that at the very start of his Associateship he will know exactly what he will have to do in order to be advanced to Fellowship.

Dr. Robert B. Radl, Governor for North Dakota, inquired concerning present age limitations in the By-Laws and rules of the College, and was informed that formerly it was required that Associates be at least twenty-six years of age and Fellows not younger than twenty-nine years of age, but with the revision of the By-Laws a year or two ago, mention of age was entirely eliminated, in view of the fact that no candidate would be able to fulfill the requirements for Fellowship under the age of thirty. It was also brought out in discussion that the Credentials Committee not infrequently received proposals of candidates for Associateship beyond sixty years of age; that the Committee has always felt that Associateship is a junior probationary status; that if a man has not arrived at a point where he is qualified for Direct Fellowship at the age of sixty or thereafter, the Committee takes the attitude that he will never be qualified and, therefore, should not be elected an Associate.

Dr. David W. Carter, Jr. (Governor for Texas): Mr. Chairman, I have had the problem, and I am sure all the Governors have likewise, of receiving reports from the Credentials Committee saying that the candidate is deferred for further seasoning, and we have not always known with what "seasoning" they should be seasoned. It would help the Governors if this period of seasoning and maturity were stated definitely—whether it is two years, three years, or whatever the Committee prescribes. I have endorsed young men whom I have known since they began to study medicine, men who have finished their residencies, who have served in the Army and Navy and come back and established themselves in practice, possibly for six months in their home town. I have felt that they were eligible, yet they were deferred.

Chairman Palmer: There is no By-Law or established rule by the Regents to the effect that the period of establishment must be two years, but this is the suggested rule of the Credentials Committee.

Dr. Lemuel C. McGee (Governor for Delaware): Mr. Chairman, in order to bring this to a vote, I would like to comment and make a motion. First, we have considerable respect for the experience that Dr. Lathrope has had in the important problems of the Credentials Committee. Likewise, we realize that a problem, such as Dr. Carter has brought up, would be simplified without our being arbitrary with the younger men if there were an age limit set. I shouldn't like to discriminate against someone by virtue of age. While age does parallel the type of development the College expects, there may be an occasional exception, which is my single reason why we might not recommend as a sentiment of this Board to the Board of Regents that the age of thirty-two be considered a minimum age for our proposals for Associateship, and I so move.

The motion was seconded by Dr. Thomas P. Murdock and opened for discussion.

Dr. Lathrope: This age limitation of thirty-two is my own idea, and I am not representing the Credentials Committee. I am not sure all of that Committee agrees with me. Many people do not, but I have been talking this for five years.

Dr. E. Dice Lineberry (Governor for Alabama): I agree most thoroughly with the idea, but I don't believe we should set an age limit. It will only take care of a very few people and penalize the occasional brilliant fellow that gets along at an earlier age. I do thoroughly approve of Dr. Yater's idea of a school for Governors. I became a Governor during the war and I did not know what it was all about. I think these new Governors are going to do a better job than those of us who came

in without instruction, other than that furnished by the Secretary. I am opposed to the age limit for membership in the College.

DR. EDGAR HULL (Governor for LOUISIANA): We should guard against Associateship or Fellowship becoming more or less automatic. The more rules we have pertaining to Board Certification, pertaining to age, pertaining to the number of papers that the candidate must write, pertaining to the number of years which he must have practiced in a community, the more apt we are to have membership in the College become automatic, in which case we would have no need for a Board of Governors and little or no need for a Committee on Credentials. Personally, I favor leaving the rules as they are and having the Governors of the College realize that they have a responsibility in determining whom they should and should not endorse for membership, and the Committee on Credentials has a similar, but even greater, responsibility. I for one am not irked at all when the Credentials Committee turns down a candidate whom I endorsed. I personally favor leaving the rules as they are, and still having the Board of Governors and the Committee on Credentials do a job.

DR. ARLESS A. BLAIR (Governor for ARKANSAS): If you put the age limit too far away from the candidate's training, he is going to find it more difficult to pass his Board examinations. That is the principal objection I have to an age limit.

DR. RADL: Under the present plan of operation, the average candidate for Fellowship qualifies possibly at the age of thirty-six. We should be careful not to deprive the younger man of the benefits of the College—the Regional Meetings, Annual Meetings, Postgraduate Courses, etc.

DR. RALPH A. KINSELLA (Governor for MISSOURI): Educational opportunity, I think, is probably more important in establishing a ceiling for admitting Associates rather than a minimal age.

The motion before the Board was now voted upon and defeated.

Chairman Palmer then asked for discussion of other problems or policies.

DR. GEORGE H. ANDERSON (Governor for WASHINGTON): Something should be done about making more seats available for members at the General Sessions. Many of us have had to stand up. Someone has thought that by raising the fee for non-members it would remedy this situation, but I contend it would accomplish nothing. I believe the guests will come anyhow.

DR. YATER: Mr. Chairman, the Credentials Committee recommended recently that attendance be limited to members and actually invited guests of members, but that suggestion was defeated at the joint meeting of the Governors and Regents on March 27. Therefore, the matter will have to be reopened if anything further is to be done about it. It seems unfortunate to me that there are so few cities in which the College can now meet for its Annual Sessions. If we could limit the non-member attendance we could get around the country better. It would be a more healthy condition for the College. In which cities can the College now be accommodated?

MR. LOVELAND: Philadelphia, Cleveland, Boston, St. Louis, Minneapolis, St. Paul, San Francisco are the only cities that have adequate auditoriums. We have never considered Atlantic City as a possibility, because it lacks hospital clinical facilities. Our great problem is the large number of guests. At this New York meeting approximately half of the doctor registration is made up of non-members.

DR. MURDOCK: I move that the Board of Governors go on record to the Board of Regents that in the future the meetings be limited only to Fellows and Associates and guests actually invited by the Fellows, Masters and Associates.

The motion was seconded by Dr. Edward C. Reifenstein, Sr., Governor for Western New York, and after discussion it was voted upon and carried.

DR. ROBERT WILSON, JR. (Governor for SOUTH CAROLINA): Mr. Chairman, it seems to me that there are several sides to the whole question—one of which is to retain the type of meeting we are having at the moment, of which every one is in

favor. Some have expressed reluctance not to invite guests, and there is much to be said for that side. Any action taken ought to be limited and regarded purely as a trial, and I would suggest that if the Regents agree with that we try it for one year and see how it works out, and not make any permanent changes in policy. The Boston meeting will offer a splendid opportunity for that trial, to see if by limiting guests we shall increase the range of places where we may hold our Annual Sessions. There are a great many physicians in and around Boston who would probably come, the same as here in New York. I would suggest and move that the action of the Governors be taken on trial for one year, and that after that, with the statistics gathered by the Executive Secretary, the Regents decide on whether or not it should be a definite policy in the future. This I make as an amendment to the previous motion.

It was seconded by Dr. Thomas P. Murdock, put to a vote and carried.

Chairman Palmer announced that the 1950 meeting place is Boston, the dates April 17–21, and asked for the sentiments of the Board of Governors with regard to the meeting place for 1951, and the Board of Governors expressed the sentiment of leaving the selection to the Board of Regents, where that authority resides.

Chairman Palmer then called attention to the fact that the terms of six of the present Governors expire with this meeting and were not eligible for re-election, because they had served the maximal period allowed under the By-Laws. These included:

Dr. Wallace M. Yater	District of Columbia
Dr. Robert M. Moore	Indiana
Dr. Edward L. Bortz	Pennsylvania (Eastern)
Dr. R. R. Snowden	Pennsylvania (Western)
Dr. John L. Caiene	South Dakota
Dr. Louis E. Viko	Utah

Dr. Palmer personally and on behalf of the Board expressed his great appreciation for the valuable and devoted services which they had given to the College, and the Board gave them a rising vote of thanks.

Adjournment.

Attest: E. R. Loveland,
Secretary

MINUTES OF THE ANNUAL BUSINESS MEETING

New York, N. Y.

March 31, 1949

The Annual Business Meeting for 1949 of the American College of Physicians was held at the Waldorf-Astoria Hotel, New York, N. Y., Thursday, March 31, 1949, convening at 2:00 p.m., with President Walter W. Palmer presiding and Mr. E. R. Loveland acting as Secretary.

President Palmer declared a quorum present.

The Secretary read abstracted Minutes of the last preceding Annual Meeting, which were approved by resolution as read.

Dr. William D. Stroud, Treasurer, presented the following annual report of the Treasurer:

"Mr. President, Masters and Fellows of the College: The details of all operations of the College for 1948, along with the Certified Public Accountant's Audit, will be published to the members through the pages of the Annals of Internal Medicine in the near future.

"During the year 1948 the College added to its General Fund $29,045.79, to its Endowment Fund $24,055.73, and received a gift in trust of $2,500.00, a second installment on an educational trust fund of $10,000.00 subscribed by Dr. A. B. Brower, one of our Fellows.

"The gross assets of the College, as of December 31, 1948, amounted to $664,158.63, divided as follows:

General Fund	$361,790.75
Endowment Fund	286,940.80
James D. Bruce Fund	10,395.83
A. Blaine Brower Fund	5,031.25

"The College operated entirely within its budget for the year. Its investments are supervised by an Investment Counselor and the Committee on Finance, and are carefully reviewed periodically. As of December 31, 1948, the College held investments at book value totalling:

Endowment Fund	$294,277.79
General Fund	187,504.22
	$481,782.01

"The current average yield as of March 10, 1949, is 4.05 per cent.

"The Board of Regents has approved a budget for 1949 calling for an estimated income of approximately $217,000.00 and an estimated expenditure of approximately $206,000.00, leaving an anticipated balance of approximately $11,000.00. The financial policies of the College are at all times conservative."

By resolution regularly moved, seconded and carried, the Treasurer's report was accepted.

Mr. E. R. Loveland presented the following annual report of the Executive Secretary:

"Mr. President, Fellows and Masters, the report of the Executive Secretary is supplementary to those of the President, Secretary-General and Treasurer.

"There has been a gradual levelling off and a return to more normal conditions this past year from those of the War and immediate post-war years. We believe the operation of the College and its activities may now be considered approaching a normal state of affairs. We observe, however, that in spite of the War and its attendant abnormalities, the College has made great strides since 1942.

"Since our last Annual Session the fine addition to our Headquarters, offices and an Assembly Room, have been concluded and occupied. Our Assembly Room will be utilized for our Postgraduate Course in Cardiovascular Disease at Philadelphia, opening on May 2. This addition was a necessity and a wise investment.

"During 1948 we conducted 28 formal Regional Meetings, largely of the single State character, but in several instances of the multi-State character. These meetings grow in their popularity and practicability. We are sure they make a real contribution to the College work.

"The ANNALS OF INTERNAL MEDICINE continues to grow in stature and in popularity, although with the increase in the subscription rate from $7.00 to $10.00 per annum, occasioned by a sharply increasing cost over the last three or four years, the circulation has maintained its level of somewhat over 12,000 copies per month. This is gratifying, for one might have anticipated a reduction.

"During September, 1948, we republished the Membership Roster. We are pleased to announce that the Board of Regents has authorized the publication of a new and entirely revised full Directory of the College during the coming summer. The cost is estimated at from $17,000.00 to $20,000.00, but we have already received

more than two thousand pre-publication orders from members at $4.00 each, thus reducing the net cost to the College. All members are urged to file their pre-publication orders with us, not only that we may know how many copies to print, but for the advantage to the member of the $4.00 pre-publication rate. The post-publication price, necessarily, will be higher.

"In general, the College's activities continue to increase enormously. Our staff must be enlarged from time to time. We have established through the years certain ideals of promptness, efficiency, etc., which we are most anxious to maintain.

"The College is most fortunate in having a group of Officers, Regents and Governors who so unselfishly give of their time and thought. I know of no organization, lay or professional, whose governing bodies, without remuneration or special prerogatives, serve so conscientiously and well.

"I have just received from the Registration Desk a report that the total registration at this moment is 5,291, of which 821 are ladies." *

By resolution, regularly moved, seconded and carried, the report was accepted.

Dr. George Morris Piersol presented the following annual report of the Secretary-General, which by resolution was formally accepted:

"Mr. President, Regents, Governors, Masters and Fellows of the College:

"*Membership:* Since the last Annual Session of this College, there have been elected 5 Masters; 257 Fellows; and 444 Associates, which brings the total membership to 6,600, divided as follows:

15	Masters
4,748	Fellows
1,837	Associates
6,600	Total

"We recently concluded a careful analysis of the specialties of members of the College as published in the 1948 Membership Roster. 81½ per cent restrict their work to Internal Medicine or one of its recognized sub-specialties; 15 per cent restrict their work to the so-called allied specialties, such as the basic sciences, pediatrics, neurology and psychiatry, etc.; slightly over 3 per cent are now retired or inactive; and less than ¼ per cent have strayed into specialties actually unrelated directly to Internal Medicine.

"*Life Members:* During the past year 77 Fellows have become Life Members of the College, bringing the total to 785, of whom 62 are deceased, leaving a balance of 723.

"*Deaths:* It is with deep regret that we report the deaths of 1 Master; 70 Fellows; and 9 Associates during this year. Their names and records are recorded in the Archives of the College.

"*Postgraduate Courses:* The Advisory Committee on Postgraduate Courses, continuing its program and expanding sometimes to new fields, organized and conducted during 1948 a total of 17 courses, with a registration of 994 physicians. The quality of these courses is constantly and individually studied, with a view to improving them year after year.

* Final Analysis of Registration:

Members	2,486	
Guest Physicians	1,471	
Guest Non-Physicians	38	
Exhibitors	665	
Ladies	967	5,627

"*Fellowships:* The College is maintaining at the present time 6 active Research Fellowships, and has voted 7 new Research Fellowships, starting July 1, 1949. The annual budget for these fellowships is approximately $20,000.00. A plan has been consummated with the W. K. Kellogg Foundation for the College to expand its fellowship program to Latin American Countries, affording an opportunity for the further training of Latin American young men for a career in teaching and research in their home lands. They will be carefully selected, brought to the United States for study for a period of one or more years, under supervision of the American College of Physicians and the Kellogg Foundation, and the Kellogg Foundation has generously agreed to supply the necessary funds.

"As gratifying as may be the above-mentioned educational activities of the College, its Annual Sessions should not be overlooked as the most significant and far-reaching contribution of the College. The current Session is a further outstanding example of what has been accomplished by a year's well coördinated effort. We are mindful of our great debt to those who have made this New York Session possible."

DR. PIERSOL: Now, Mr. President, through this past year you have guided the destiny of this organization and have carried out its purposes with good judgment and exceptional ability. Those of us whose privilege it has been to be closely associated with you in the conduct of the College are keenly aware of the never failing courtesy, forbearance and coöperation that have marked your every act. Therefore, it is our desire to express to you in some enduring way our appreciation and affection, and so, on behalf of your fellow Officers, the Regents and Governors of the American College of Physicians, it is our pleasure at the present time to present you with this gavel. (Applause.)

PRESIDENT PALMER: Dr. Piersol, I do appreciate this recognition, and I shall treasure this token as long as I live. I do want to say this to the College. I do not know of any year in my life which has been so instructive, so illuminating and so valuable as I have had in my association with the College members, particularly in the Regional Meetings. I have gotten an entirely different idea of what the College means to its members.

Before relinquishing my Presidency and introducing your new President, I should like to say a few words about him. At the end of my second year in Harvard Medical School his father gave the first clinic that I ever attended. It was a clinic which I shall never forget. Dr. Fitz' father was a master of presentation and stimulation in this work. Later on I had the pleasure to serve with Dr. Fitz, your new President, as Associate at Massachusetts General Hospital. He was a year ahead of me, and I always valued his association greatly. After he graduated from the Massachusetts General Hospital he served as assistant resident at Hopkins, then went back to Brigham and then to the Rockefeller Hospital as assistant resident and finally as resident at Massachusetts General. During World War I he served in the Army as a Medical Officer. He spent the years 1920 through 1922 at the Mayo Clinic, later coming back to Boston as the Director of the Medical Service, associated with Boston University, and thereafter arriving at his position in the Harvard Medical School in 1929 as a Lecturer in the History of Medicine and Assistant to the Dean.

Dr. Fitz has served the College long and well. He conducted the clinical program in Rochester, Minn., at the Sixth Annual Session of the College. Nineteen years later he performed a similar function in Boston. For years he has been on the Board of Regents. He has been Chairman of several of their Committees, and is an efficient Chairman. It is with great pleasure that I introduce my old friend and colleague, Dr. Reginald Fitz, your new President.

(The members arose and applauded.)

Dr. Fitz assumed the Chair.

DR. REGINALD FITZ: Dr. Palmer, it is very interesting that I have always been proud of the fact that I was ahead of you, and now I continue to be proud that I can be a year behind you, helping to carry forward the example and the judgment and the enthusiasm that you have shown in being President of the College.

I think that any man who has the honor of being elected to the Presidency of the American College of Physicians just feels that he has been paid the greatest compliment that can be given to any internist in the country, and for me now to realize that I am President of the College, President of a group of 6,600 colleagues, all of whom are interested in advancing the field of Internal Medicine, is a great compliment and also an extremely serious, heavy responsibility.

All I can say is that I have entered into this office realizing that, and all I can say to you is that I promise to carry forward the aims of the College, the work of the College and to do the best I can during the ensuing year for the benefit of the American College of Physicians.

President Fitz then called upon the Secretary to present an amendment to the Constitution and By-Laws.

SECRETARY E. R. LOVELAND: The Board of Regents of the American College of Physicians on November 7, 1948, formally adopted a resolution recommending the following amendments to the Constitution and By-Laws, to provide for Honorary Fellows.

Constitution, Article IV, to be amended by changing the introductory sentence to read: "Members of the American College of Physicians shall be of three classes: (a) Fellows; (b) Masters; and (c) Honorary Fellows."

By adding a new Section to Article IV as follows: "(c). Honorary Fellows. Honorary Fellows shall be internists, members of the medical profession of countries other than the United States or Canada, who on account of personal character, positions of honor and influence, or eminence in the practice of internal medicine or in research, shall be recommended by the Committee on Masterships to the Board of Regents. Honorary Fellows shall not have the right to vote or to hold office."

Article IV, Section (b), shall be amended by reversing the order of the words "influence and honor" to read "honor and influence."

By-Laws, Article VI, the title to be amended to read, "Election of Masters and Honorary Fellows"; also by numbering the first paragraph "(a)", and adding paragraph "(b). The Committee on Masterships may also present to the Board of Regents nominations for the election of Honorary Fellows. Not more than two Honorary Fellows shall be elected in any calendar year."

It was regularly moved, seconded and unanimously carried, that the recommended amendments be adopted.

President Fitz then asked for the report of the Committee on Nominations, Dr. Maurice C. Pincoffs, Chairman.

MAURICE C. PINCOFFS: The Committee on Nominations, appointed in accordance with the Constitution of the College, places in nomination the following names for the Elective Officers of the College:

For President-Elect	Dr. William S. Middleton, Madison, Wis.
For First Vice President	Dr. George F. Strong, Vancouver, B. C., Canada
For Second Vice President	Dr. Roy R. Snowden, Pittsburgh, Pa.
For Third Vice President	Dr. Turner Z. Cason, Jacksonville, Fla.

The election of these nominees as Officers was moved by Dr. Maurice C. Pincoffs, and duly seconded.

The Chairman inquired for nominations from the floor; there being none, a motion was made, seconded and carried instructing the Secretary to cast a single ballot for the election of all the above Officers.

DR. PINCOFFS (Continuing): The Committee places in nomination five names for election as Regents of the American College of Physicians, for a term expiring in 1952:

Dr. William S. McCann, Rochester, N. Y.
Dr. T. Grier Miller, Philadelphia, Pa.
Dr. Charles F. Moffatt, Montreal, Que., Canada
Dr. Harold H. Jones, Winfield, Kans.
Dr. Edward L. Bortz, Philadelphia, Pa.

The Committee further places in nomination for election as Regent for a term expiring in 1951 the name of:

Dr. Wallace M. Yater, Washington, D. C.

The election of these Regents was moved by Dr. Maurice C. Pincoffs, and duly seconded.

President Fitz called for nominations from the floor; there being none, a motion was made, seconded and carried, instructing the Secretary to cast a single ballot for the election of all the above Regents.

DR. PINCOFFS (Continuing): The Committee places in nomination the names of the following men as Governors of the American College of Physicians for a term expiring in 1952:

Dr. Leland Hawkins, Los Angeles .....CALIFORNIA (Southern)
Dr. Ward Darley, Denver .....COLORADO
Dr. Thomas P. Murdock, Meriden .....CONNECTICUT
Dr. John Minor, Washington .....DISTRICT OF COLUMBIA
Dr. Cecil M. Jack, Decatur .....ILLINOIS (Southern)
Dr. James O. Ritchey, Indianapolis .....INDIANA
Dr. William C. Menninger, Topeka .....KANSAS
Dr. Chester S. Keefer, Boston .....MASSACHUSETTS
Dr. Joseph D. McCarthy, Omaha .....NEBRASKA
Dr. Edward C. Reifenstein, Sr., Syracuse...NEW YORK (Western)
Dr. Wann Langston, Oklahoma City .....OKLAHOMA
Dr. Thomas M. McMillan, Philadelphia ....PENNSYLVANIA (Eastern)
Dr. Charles W. Morton, Pittsburgh .....PENNSYLVANIA (Western)
Dr. Charles F. Morsman, Hot Springs .....SOUTH DAKOTA
Dr. William C. Chaney, Memphis .....TENNESSEE
Dr. Fuller B. Bailey, Salt Lake City .....UTAH
Dr. Nils P. Larsen, Honolulu .....HAWAII
Dr. Herbert K. Detweiler, Toronto .....ONTARIO
Dr. Francisco de P. Miranda, Mexico City .MEXICO
Dr. Gilbert M. Stevenson, Ancon .....REPUBLIC OF PANAMA and the CANAL ZONE

In addition, the Committee nominates as Governor for a term expiring in 1951:

Dr. Walter I. Werner, Albuquerque .....NEW MEXICO

The election of these Governors was moved by Dr. Maurice C. Pincoffs and duly seconded.

President Fitz called for nominations from the floor; there being none, a motion was made, seconded and carried, instructing the Secretary to cast a single ballot for the election of all the above Governors.

The Secretary announced the casting of the ballot for the election of all nominees as presented by the Committee on Nominations, which consisted of:

Dr. Maurice C. Pincoffs, Chairman .....Regent
Dr. A. B. Brower .....Regent
Dr. Chester S. Keefer .....Governor
Dr. Harold H. Jones .....Governor
Dr. T. Homer Coffen .....Fellow-at-Large

President Fitz appointed Dr. Charles T. Stone and Dr. S. Marx White as a Committee of Two to escort the new President-Elect, Dr. William S. Middleton, to the platform.

(The audience arose and applauded.)

DR. WILLIAM S. MIDDLETON: Mr. President, Masters and Fellows of the College: I am deeply conscious of the honor of this election. I am indeed humble in your expression of confidence. As an ambassador without portfolio, I pledge my best efforts to the high ideals of the American College of Physicians, and to the interest of American medicine. I thank you. (Prolonged applause.)

PRESIDENT FITZ: We are going through one of the biggest and most important sessions that the College has ever had, and already we are thinking of our next Annual Session. I announce to you that the 1950 Annual Session will be held in Boston, Mass., and the dates will be April 17–21. I am sure that the City of Boston is looking forward to having the College come, but if the College attendance is as large in Boston as it has been in New York, I cannot imagine what will be left of Boston when the College leaves.

Dr. F. Gorham Brigham at this point offered the following resolution of thanks:

"To our distinguished leader and President, Dr. Walter W. Palmer, for the inspiration of his guidance during the past year, as well as during this Annual Session:

"To his Chief of Staff, General Chairman Franklin M. Hanger, for a magnificent program;

"To the Chairman of their local Committees:

Dr. Theodore B. Russell, Chairman of the Committee on Auditorium
Dr. Harold J. Stewart, Chairman of the Committee on Clinics
Dr. Ralph H. Boots, Chairman of the Committee on Entertainment
Dr. Carl Muschenheim, Chairman of the Committee on Hotels and Transportation
Dr. Alexander B. Gutman, Chairman of the Committee on Panel Discussions
Dr. Howard A. Rusk, Chairman of the Committee on Publicity

and to the individual members of each of those Committees;

"To Mrs. Edgar Stillman, Chairman of the Committee on Women's Entertainment, and all of her worthy and capable colleagues;

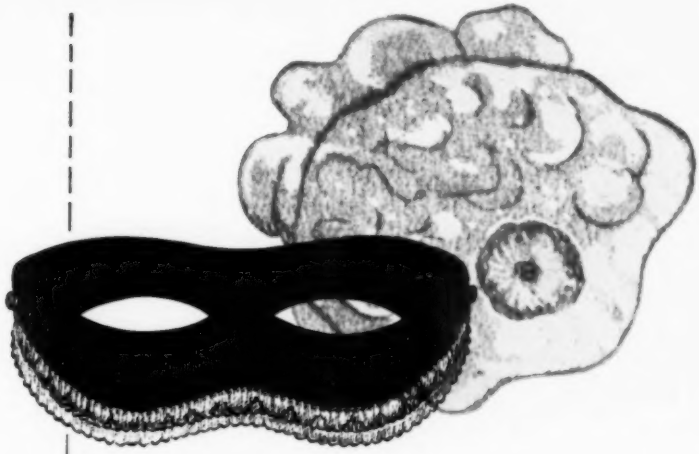
"To Mr. Royal W. Ryan, Executive Vice President of the New York Convention and Visitors Bureau;

"To all of these and many others, individually and collectively, our heartfelt thanks again for their generous hospitality in full measure—pressed down and running over."

Amid applause, the resolution was seconded and unanimously carried.

Adjournment, 3:15 p.m.

Attest: E. R. LOVELAND,
Secretary



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*Robinson, R. A.: Amebiasis, South. Med. J. 39:876 (Nov.) 1946.

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4. Doe, J. E.: What I know about it, Jr. Am. Med. Assoc., 1931, xcvi, 2006–2008.

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